This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

+ *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.

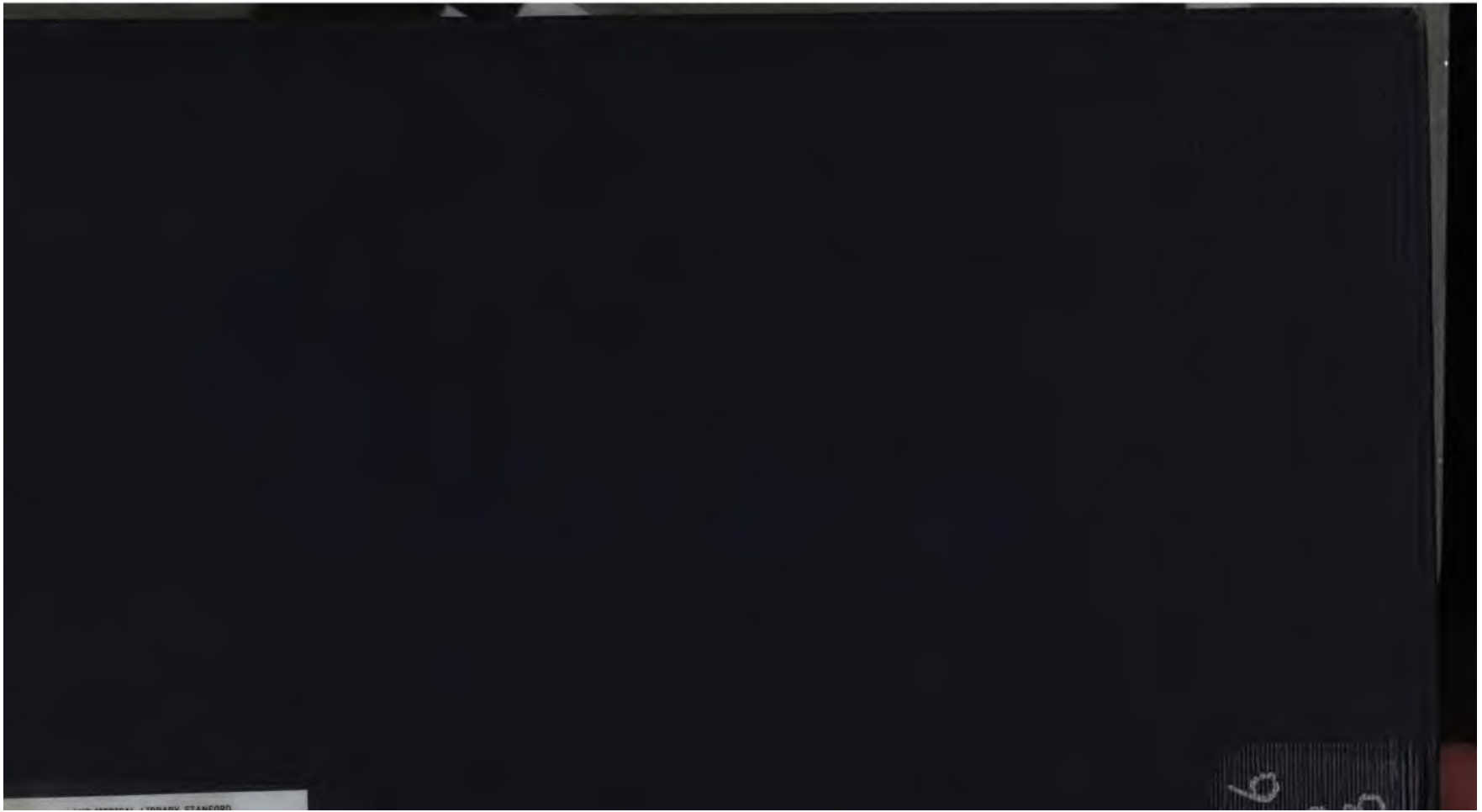
+ *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.

+ *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.

+ *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

About Google Book Search

Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at `http://books.google.com/`



LANE

MEDICAL LIBRARY

LUTHER JANNA HOUTON FUND

COPYRIGHT, 1913, BY C. V. MOSBY COMPANY

LANE LIBRARY

Press of
C. V. Mosby Company
St. Louis

.U796
P86
1913

TUBERCULIN IN DIAGNOSIS AND TREATMENT

41170

CONTENTS.

CHAPTER I.

IMPORTANCE OF THE TUBERCULIN TEST IN THE EARLY DIAGNOSIS OF TUBERCULOSIS.

Page

Effect of Sputum Examination on Diagnosis—Effect of the Tuberculin Test on Diagnosis—Cause of Tuberculin Reaction—Value of the Tuberculin Test—Tuberculin Test Not a Test for Tuberculosis but for Tuberculosis Antibodies—Specificity of Tuberculin—What Information Does the Tuberculin Test Furnish?—Latent Tuberculosis Dangerous—Receptive Capacity of Patients Differ—Diagnostic Value of Nature of Reaction—Tuberculin Reaction May be Negative Immediately Following an Initial Hemorrhage—Interpretation of the Tuberculin Test 1–15

CHAPTER II.

SUBCUTANEOUS TUBERCULIN TEST.

Original Fear of Test—Tuberculin Reaction—Local Reaction—General Reaction—Focal Reaction—Selection of Tuberculin for the Subcutaneous Test—Dilution of Tuberculin—Method of Making Dilutions—Applicability of the Subcutaneous Tuberculin Test in Early Tuberculosis—Healing Stimulated by Reaction—What is Necessary Before Giving the Subcutaneous Test—Technic of Administration—Dosage—Maximum Dose—Tuberculous Patients May Not React 16–28

CHAPTER III.

CUTANEOUS TUBERCULIN TEST.

Importance of the Cutaneous Reaction—Infection Takes Place in Childhood—Specificity of the Cutaneous Reaction—Conditions Under Which the Cutaneous Reaction Does Not Occur—Traumatic Reaction—Positive Reaction—Negative Reaction—Interpretation of the Reaction—Theoretical Grounds for Cutaneous Tuberculin Test Differentiating Between Active and Quiescent Tuberculosis—The Prognostic Importance of the Cutaneous Test—Technic—Tuberculin Used 29–44

CHAPTER IV.

PERCUTANEOUS TUBERCULIN TEST.

Character of the Reaction—Test of Lignières 45–46

CONTENTS.

CHAPTER V.

CONJUNCTIVAL TUBERCULIN TEST.

Page

Technic—Solution Used—Conjunctival Reaction—Contraindications —Repetition of Test—Negative Reaction—Conjunctival Reaction and Active Tuberculosis—Specificity of the Conjunctival Test . 47–50

CHAPTER VI.

TUBERCULIN IN THE TREATMENT OF TUBERCULOSIS.

Tuberculin as a Therapeutic Measure Well Established—Tuberculin Not a Poison—Tuberculin Misunderstood—Tuberculin Infection —Infection and Immunity—Evidences of Immunity in Tuberculosis—Artificial Immunity in Animals—Artificial Immunity in Human Beings—Latency—Curability of Latent and Early Active Tuberculosis—Action of Tuberculin—Why Use Tuberculin Where Spontaneous Cure Fails?—Autotuberculin Therapy—Negative Phase—Tuberculin Difficult of Administration—Length of Time of Treatment—Indications and Contraindications for the Use of Tuberculin—Tuberculin Active Immunizer—Rapidly Progressive Cases—Indiscriminate Treatment Not Favored—Mixed Infection—Hemorrhage—Rapid Pulse—Organic and Constitutional Diseases 51–89

CHAPTER VII.

Hypersensitiveness 90–95

CHAPTER VIII.

CERTAIN CONDITIONS WHICH HAVE MADE THE ADOPTION OF TUBERCULIN AS A DIAGNOSTIC AND THERAPEUTIC MEASURE DIFFICULT.

The Disaster of 1890–91—Immunizing Power of Tuberculin Shown by Animal Experiment—Lack of Knowledge of Tuberculin—Lack of Knowledge Concerning Tuberculosis—Lack of Unanimity of Opinion of Friends 96–114

CHAPTER IX.

EVIDENCES OF THE THERAPEUTIC VALUE OF TUBERCULIN.

Tuberculin Increases the Percentage of Cures—Tuberculin Prevents the Spread of Infection—Fewer Complications—Tuberculin Shortens the Term of Treatment—Tuberculous Complications Heal More Readily—Pleural Effusion—Tuberculosis of the Larynx —Tuberculosis of the Intestine—Tuberculosis of the Lymphatic Glands—Genitourinary Tuberculosis—Tuberculosis of the Ear—Tuberculosis of the Eye—Eczema—Tuberculin Prevents Relapses —Experimental Proof of the Value of Tuberculin 115–126

CONTENTS.

CHAPTER X.

FEVER IN ITS RELATIONSHIP TO TUBERCULOSIS.

Page
Cause of Fever 127–135

CHAPTER XI.

TEMPERATURE CURVE IN TUBERCULOSIS.

Normal Curve—Temperature Curve in Tuberculosis—Temperature Curve as Affected by Autolysis—Curve in Mixed Infection—Cause of Chill or Rigor—Factors Interfering with the Regular Curve—Physical and Mental Exertion—Premenstrual Fever—Characteristics of the Temperature Curve Due to Tuberculin Reaction 136–150

CHAPTER XII.

TECHNIC OF ADMINISTERING TUBERCULIN.

Choice of a Preparation—Preparations Which are Most Commonly Used—Bovine Tuberculin—Method of Administration—Method of Diluting Tuberculin—Tuberculin Made from Different Strains of Bacilli and Grown on Different Media Differ—Physicians Should Know the Value in Milligrams or Cubic Millimeters of Each Dose—Cubic Millimeter as Unit of Dosage—Schemata—Syringe—Time of Day of Injection—Tuberculin Tray—How to Avoid Errors in Dosage—Site of Injection—Local Reactions Where Previous Inoculations Have Been Given—Initial Dose and Method of Increasing—Interval Between Dosage—Maximum Dose—Duration of Treatment—After-Course of Tuberculin—When to Avoid Focal Reaction—When to Produce Focal Reaction—Necessity of Controlling Doses by the Extent of the Focal Reaction—Importance of Minute Records of Chest Examinations for Comparison—Value of the Graphic Temperature Chart—How are we to Judge the Value of Tuberculin—Reduction of Tubercle Bacilli in the Sputum—When Reaction Occurs, What Shall be the Next Dose?—Are There Patients Suffering from Tuberculosis Who Cannot be Treated with Tuberculin?—When to Withhold Dosage During Treatment—What is the Guide to Dosage?—Observation and Control of Patient—How Tell When a Patient is Well?—Relative Merits of Sanatoria, Homes, and Dispensaries in the Treatment of Tuberculosis—Sanatorium—Home Treatment—Dispensaries—Necessity of Isolating the Open Cases—Who Must Administer Tuberculin?—Should the Patient be Allowed to Treat Himself?—When Should Tuberculin Begin in Fever Cases?—Method of Dosage in Early Tuberculosis—Treatment of Tuberculosis with Fever—Use of Tuberculin in Children—Passive Immunization 151–215

APPENDIX.

Koch's Announcement of the Discovery of Tuberculin—Further Report on a Remedy for Tuberculosis—Still Further Report on a Remedy for Tuberculosis 219–231

ILLUSTRATIONS.

		Page
Plate I.	Conjunctival, Moro, and von Pirquet reactions . .	*Frontispiece*
Fig. 1.	Temperature curve of tuberculin reaction	19
2A.	von Pirquet scarifier	42
2B.	Scarifier made by H. M. Alexander & Co.	42
3.	Illustrating method of making cutaneous test	43
4.	Rapid pulse. Patient making satisfactory improvement . .	87
5.	Temperature curve of acute miliary tuberculosis	131
6.	Curves showing normal daily variation in temperature (Jurgensen)	137
7.	Temperature curve of acute miliary tuberculosis ingrafted on a chronic process	137
8.	Temperature curve of early pulmonary tuberculosis . . .	138
9.	Temperature curve of chronic fibroid tuberculosis	138
10.	Temperature curve of quiescent chronic ulcerative tuberculosis	138
11.	Temperature curve of chronic ulcerative tuberculosis with moderate activity	139
12.	Temperature curve of moderate degree of autolysis . . .	139
13.	Three months' temperature curve of patient showing moderate degree of autolysis	140
14.	Temperature curve of marked autolysis	141
15.	Temperature curve of mixed infection, also showing effect of baths on temperature curve	141
16.	Illustrating how temperature curve is influenced by atmospheric temperature	144
17.	Illustrating effect of overexertion in chronic inactive tuberculosis	145
18.	Illustrating the effect of overexertion in chronic active tuberculosis	145
19.	Illustrating effect of worry on temperature curve	146
20.	Illustrating effect of acute gastroenteritis on curve of chronic active tuberculosis	146
21.	Illustrating premenstrual rise in temperature curve . . .	147
22.	Temperature curves due to tuberculin reactions	149
23.	Temperature curve of secondary tuberculin reaction . . .	149
24.	Temperature curve due to natural inflammation of tuberculosis areas	150
25.	Record and Luer syringes	168
26A.	Illustrating method of fixing piston of syringe with first finger	168
26B.	Illustrating method of injecting tuberculin with same finger	168
27.	Tuberculin tray	170
28.	Schematic representation of phenomena following doses of tuberculin	177
29.	Schematic representation of (1) repeated small doses, (2) production of toximmunity	179
30A.	Illustrating method of recording ausculatory findings . .	186
30B.	Illustrating method of recording ausculatory findings . .	187
31.	Graphic chart for temperature and pulse with record of symptoms added	188

Page

Fig. 32. Temperature curve of chronic active tuberculosis, with repeated attacks of high temperature, treated with tuberculin 207

33. Showing marked rises of temperature due to small ulceration in the pharynx 208

34. Temperature curve of chronic tuberculosis with occasional rises of temperature illustrating difficulties in interpreting cause of temperature rises 210

INTRODUCTION.

I assume the task of writing a monograph on the diagnostic and therapeutic use of tuberculin with hesitation, because I realize the importance of the subject and the many things in the way of giving to my readers something definite and tangible.

The demand for such a monograph is the motive which causes me to undertake the work, and the fact of my long and extensive experience in the employment of tuberculin in the diagnosis and treatment of tuberculosis is the fact which warrants my doing so.

When first I became interested in the treatment of tuberculosis I was directed by Dr. Karl von Ruck into the study of its cure from the standpoint of the production of immunity. Through his guidance I took up the administration of tuberculin at a time when it was very unpopular.

Following the disaster attending the early use of tuberculin, the prejudice against it was so great that those who persisted in employing it were looked upon with disfavor by other members of the profession; but after careful, painstaking work these observers were able to show by the results obtained that tuberculin, when administered properly, is of great value in promoting the healing of tuberculosis; and as a result of their labors, the remedy has come into all but general use.

The rapidity with which tuberculin is gaining supporters is indicated by its increased popularity in the German sanatoria. In making a tour of these institutions, in 1905, I found considerable hostility to tuberculin and noted that only about 25 per cent were employing it therapeutically. In 1909, I made another visit and found that about two thirds of them were using it.

I gave my first dose of tuberculin on January 9, 1896. From then until now there has never been a time when I have not had from a few to more than a hundred patients under treatment. Altogether I have gained my experience in the use of tuberculin by treating about two thousand patients. These patients have

represented all stages of the disease, nearly every phase of pathological change found in tuberculosis, and complications on the part of all organs and parts of the body. I have been particularly fortunate in that my patients have been for the most part private cases of a high degree of intelligence, whose co-operation has added much to the satisfaction and success of treatment. Nearly all of them have been treated in a private sanatorium, where conditions were ideal and where my close association with them enabled me to adapt the remedy to each case and to carefully study the effect of each dose.

Another factor which has contributed largely to my success in the employment of tuberculin is the fact that I have always taken a broad view of tuberculosis and its treatment. While I have been an ardent supporter of tuberculin, I have always reinforced it by every measure that would improve the physical and mental condition of the patient. The injection of tuberculin is not treating tuberculosis. Tuberculin acts only on the tuberculous process and affects the general well-being of the patient indirectly; general hygienic and tonic measures and those which improve the mental condition of the patient, on the other hand, affect every organ and function of the body and act upon the tuberculous process indirectly. The two are supplementary, and both essential to best results.

In spite of the long use of tuberculin there are many things about it which are poorly understood. There are many questions still unanswered. Our only working basis is theory as yet and may be changed at any time. Nevertheless, we now have sufficient clinical experience at hand on which to base a rational administration of the remedy.

Ever since the discovery of tuberculin, but especially since its revival and more general introduction into medical practice, there has been a demand for an exact schema showing how tuberculin may be given by rule, increasing the dose with a certain definitely stated rapidity and at definitely stated intervals. Those who expect this will be disappointed, for tuberculin cannot be given to best advantage in such a manner. I have attempted, however, to explain the nature of tuberculin and the ways in which it acts and to show the nature of tuberculosis and the method of its healing so that any one who will study the

text may sufficiently familiarize himself with the principles of tuberculin therapy to be able to employ it intelligently.

While there are objections to the general employment of tuberculin by physicians who are not making a special study of tuberculosis, yet the time is near at hand when many of the simpler cases, at least, will be treated by the general practitioner. The success which will attend this plan will depend on the intelligence with which it is undertaken. I hope that I have been able to give a sufficiently clear discussion of the subject in this monograph to help anyone who is earnestly trying to learn the intelligent employment of the remedy; if so, my work will not have been in vain.

A certain amount of repetition appears in the text. This was done, sometimes for emphasis, and at other times for clearness. In discussing a question with so many phases this seemed unavoidable. I hope, however, that it will add to the value of the book and not detract from its usefulness. My readers must bear in mind that the subject treated in this monograph is constantly unfolding. New theories are being advanced, and new knowledge added each year. I trust that many of the points which seem unsettled now will soon be disproved or established so that tuberculin may find its true place as a diagnostic and therapeutic agent. It is impossible for me to give due credit for all of the ideas expressed in this work. I have been a wide reader of the best literature on tuberculin. I have visited many of the world's foremost workers in tuberculin therapy, and besides have had my own long experience. I have not attempted to give a large bibliography or quote extensively, but have discussed the subject as I see it after having my ideas formed and influenced by books, men, and experience. For whatever of merit or fault this monograph contains, I alone assume the responsibility.

I am indebted to George S. Lacy for making the charts, and otherwise assisting in the preparation of the illustrations.

Monrovia, California.

February, 1913.

TUBERCULIN IN DIAGNOSIS AND TREATMENT.

CHAPTER I.

IMPORTANCE OF THE TUBERCULIN TEST IN THE EARLY DIAGNOSIS OF TUBERCULOSIS.

The first great advance in the diagnosis of tuberculosis was made possible by Koch's discovery of the tubercle bacillus. Prior to this, tuberculosis was generally recognized as a fatal disease; it was not diagnosed until the symptoms were marked, and then the death of the patient was required to substantiate the diagnosis. A restoration to health was a sure sign of error in diagnosis. While there were a few exceptions to this rule—a few who dared believe that tuberculosis could at times be healed—they were so clearly in the minority that they made little impression upon the general pessimistic attitude of the time.

Effect of Sputum Examination on Diagnosis.—The finding of tubercle bacilli was soon required for a diagnosis, and for a considerable time a positive or negative diagnosis depended upon the presence or absence of the tubercle bacillus in the discharges from the diseased focus. This created a new interest in diagnosis. It was soon found that an individual might have the diagnosis of tuberculosis confirmed by the finding of tubercle bacilli and still regain health and be a useful citizen. By studying these favorable cases it was further found that there were certain symptoms and physical signs which were present that differed from the grave symptoms and marked physical signs which attended the fatal cases which had previously been recognized as tuberculosis. These symptoms and signs were soon classified as those which go to make up the picture of early tuberculosis. This proved to be a wonderful advance in clinical diagnosis and settled the matter definitely that tuberculosis, when detected early,

is curable, but when detected late, is usually fatal. This, likewise, gave increased impetus to the movement for the cure of tuberculosis.

Effect of the Tuberculin Test on Diagnosis.—The next advance in diagnosis was made when it was shown by Koch that tuberculin caused a reaction in those suffering from tuberculosis but did not in those free from the disease. Practically all of the genuine advance in truly early diagnosis and the magnificent results in the treatment of tuberculosis are attributable to the effect of these two discoveries: the tubercle bacillus, and the tuberculin reaction.

While some physicians still hold to the opinion that the finding of tubercle bacilli is the only sure and dependable proof of the presence of clinical tuberculosis, yet they are in the great minority. The great majority of our progressive men recognize that our new methods of examination enable us to make a correct diagnosis in nearly all instances without depending upon the presence or absence of bacilli. It is fortunate that this is true; for, when the disease has gone on to the point of ulceration and discharge of bacilli, the tuberculous foci are no longer closed, and the chances of cure are considerably reduced. While we must admit that there is some error in diagnosis in these early cases, yet the error is reduced to a minimum when made by an expert examiner, and in all instances, is no greater than that incident to many other diseases. And further, the question at issue is, as a rule, not whether tuberculosis is present, but whether or not it is active. The positively non-tuberculous cases can, as a rule, be excluded with almost absolute certainty. Whatever error is made should be on the side of positive rather than negative diagnosis; for, while the one submits the patient to some annoyance and expense, the other endangers life. If care be exercised the percentage of error need be very small.

While the examination for tubercle bacilli stimulated earlier diagnosis, and a greater interest in the cure of tuberculosis, the tuberculin test has made possible the diagnosis before bacilli appear in the discharges. Not only has it done this, but to the influence of this test may we assign much of our advance in the study of tuberculous infection, and of tuberculosis as a clinical manifestation, as well as the fact that it is now looked upon as

a comparatively curable disease. To the knowledge derived from applying this test we are also indebted for a better appreciation of the problems of its prevention.

Cause of Tuberculin Reaction.—Koch was originally of the opinion that the tuberculin reaction is due to adding the injected tuberculin to the toxins which already exist in the body, and the increased amount of toxins, being more than the organism can bear, caused the toxic symptoms to appear.

Ehrlich suggests that the tuberculin reaction takes place in the middle of the three layers of cells which surround the tuberculous focus.

Wassermann and Bruck,[1] by studying the deviation of the complement, have found a substance which with tuberculin causes absorption of the complement. This they have called antituberculin. It is found both in the blood and in the foci of infection of those who are treated with tuberculin. They consider that the reaction caused by tuberculin takes place in the tuberculous focus and is a result of the combination of tuberculin and antituberculin, and that the ill effects resulting from excessive doses as well as the beneficial stimulating effect are a result of the complement fixation. The fever and attending clinical symptoms are secondary to the focal reaction. According to this theory, if free antituberculin is found in the blood in sufficient amounts to neutralize the tuberculin injected, none of it will reach the tuberculous focus, and no reaction will occur; if, on the other hand, an excess of tuberculin should be injected, the excess would reach the focus of infection and produce a reaction. This theory supposes that the focal reaction is secondary in the natural healing and that it occurs only in case there is an excess of tuberculin over the antituberculin. While ingenious, this theory does not seem to explain everything satisfactorily.

Marmorek is of the opinion that the tubercle bacilli, stimulated by the injection of the tuberculin, secrete fever-producing bodies.

Von Pirquet and Schick hold that the tuberculin reaction is due to the formation of toxic substances as a result of the combination of the antibodies circulating in the blood, and the tuberculin. This occurs both at the point of inoculation, produc-

[1] *Deutsche medizinische Wochenschrift*, 1906, Nr. 12.

ing a local reaction, and in the circulation, producing a general reaction.

Wolff-Eisner's theory is akin to the theory of von Pirquet and Schick. His conception is that tuberculin, no matter what preparation is used, depends for its activity upon the fact that bodies, or portions of bodies of tubercle bacilli, are present in the preparation. He considers that the stimulating principle is the protein of the bacillus, whether from living bacilli or dead bacilli as represented by the tuberculin preparation. He believes that the reaction which takes place when tuberculin is introduced is produced by the action of the same lysins which cause the bodies of the tubercle bacilli to go into solution. As a result of this lysis, endotoxins are set free which produce the tuberculin reaction. This conception is a double one. It presumes that there are two factors in tuberculosis immunity: first, a lysis; and second, an antitoxic action. The first destroys the bacilli. The second renders the toxins which are set free harmless. We shall discuss this theory more fully later, in connection with the action of tuberculin when used as a test or therapeutically (pages 37, 67).

Taking Wolff-Eisner's theory as a basis and adding a few suggestions from other writers, we can offer a fairly satisfactory explanation of nearly all phenomena that occur when tuberculin is brought in contact with the living tissues, whether it be in one of the tuberculin tests or when employed therapeutically.

The points of most importance as I see them, and as I shall discuss them throughout the monograph, are as follows:

1. Tuberculin is not a poison but a specific substance which, when given in large doses, unless the patient has had his tolerance increased by previous doses, causes toxic symptoms (reaction) in one suffering from tuberculosis. In the healthy large doses can be borne without harm resulting.

2. The specific products of all preparations of tuberculin differ quantitatively, but qualitatively they are the same.

3. The specific action is due to the tubercle protein contained in the product and follows the general laws of hypersensibility of an organism to foreign protein (serum disease).

4. The action of the tubercle protein as it causes reaction in the presence of tuberculosis, whether used as a test or therapeutically, is modified by the fact that the organism has been

sensitized to the protein as given off from the focus of infection.

5. The specific immune bodies found in tuberculosis are present either fixed to the cells or circulating in the body fluids.

Value of the Tuberculin Test.—Not the least important of the services rendered by the tuberculin test is the appreciation of the fact that infection occurs early in life, the disease assuming a condition of latency in those instances where it does not quickly destroy the patient or go on to a healing. Study of this condition of latency has brought about a complete change in our ideas of tuberculosis. The weight of evidence is against its being the harmless condition which we had previously thought, for the evidence is now strong that most instances of clinical tuberculosis in adults are due to renewed activity in previously latent foci.[2]

In order that tuberculosis may be classed as a disease which will yield to treatment to any considerable degree, two things are essential: first, an early diagnosis; second, prompt, intelligent treatment under conditions as nearly ideal as possible. If we are to have these two conditions, an understanding of tuberculin both as it is applied as a test and as a therapeutic measure is essential.

Tuberculin as a test in the diagnosis of tuberculosis was made possible by Koch's early discovery that tubercle bacilli, and their toxins, affect the tuberculous and non-tuberculous differently. In his second communication, which was his first extensive publication on the subject of tuberculosis,[3] after describing the reaction which follows the injection of tuberculin, in small doses, under the skin of human beings suffering from tuberculosis, Koch states: "The reaction phenomena just described have appeared without exception whenever a tuberculous process has been present in any portion of the body, and I am of the opinion that it is not going too far when I state that this procedure will become an indispensable diagnostic measure in the future." (See Appendix, page 223.)

Tuberculin Test Not a Test for Tuberculosis but for Tuberculosis Antibodies.—What is known as the tuberculin test consists

[2] Pottenger: The Relationship Between the Infection in the Child and Clinical Tuberculosis in the Adult, *The American Journal of Diseases of Children*, July, 1912, vol. 4, pp. 13–19.

[3] Koch: Weitere Mitteilungen über ein Heilmittel gegen Tuberkulose, *Deutsche medizinische Wochenschrift*, 1890, Nr. 46a.

in bringing tuberculin in contact with the body tissues. This may be done by injecting it under the skin, into a vein, by rubbing it into the skin or into a scarified area of the skin, or by bringing it in contact with the mucous membranes—such as the conjunctiva, nose, bronchial mucous membrane, vagina, or rectum. The essential feature of the test is that a sufficient amount of tuberculin be brought in contact with the tissues and remain in contact sufficiently long. If tuberculosis is present, barring some exceptions which will be mentioned later (pages 12, 31), a reaction occurs. If tuberculosis is not present, no reaction occurs.

In order to have the correct understanding of the tuberculin test, and in order to know why reactions sometimes fail to appear even when tuberculosis is present, it is necessary to bear in mind that the test is not a test for tuberculosis, but a test for the presence of tuberculosis antibodies. Thus, if the body cells are unable to respond to the stimulation of the protein which escapes from the tuberculous focus, and produce immune bodies, infection might be present, and yet no reaction take place when the test is applied. It is also possible that antibodies might be present and not be free in the blood, and thus cause a failure to react. The more I study the tuberculin reaction, the more I believe that not only antibodies but free-circulating antibodies are necessary to a marked reaction such as we are wont to recognize clinically, especially in the local reactions. It is also possible that lysins might be present in sufficient quantities to destroy the tuberculin, and the cells fail to respond to the stimulation of the toxins.

Specificity of Tuberculin.—Before discussing the question of the tuberculin reaction, we must emphasize the fact that tuberculin is specific in its action. While this has been called in question at times, because it seemed that the reacting patient was suffering from disease other than tuberculosis, notably syphilis, yet, when we recognize the wide distribution of tuberculous infection and the almost universal testimony, both experimental and clinical, as to the specificity of the reaction, we are forced to believe that tuberculosis was also present. It is possible that diseases caused by other acid-fast bacilli might also react to tuberculin, but these are so rare that the fact is of little importance from a diagnostic standpoint in general medicine. We are

safe in saying that the tuberculin test is specific for tuberculosis antibodies and that when a reaction occurs after the administration of any one of the tests tuberculosis is positively present.

This fact was the first that gave importance to the test. It is also the one which has threatened its reliability in furnishing evidence considered of value in the diagnosis of what we have chosen to term active tuberculosis.

What Information Does the Tuberculin Test Furnish?—By the results of post mortems we were convinced several years ago that tuberculosis is a wide-spread infection, but we had been wont to interpret the tuberculin test as a positive proof that active tuberculosis was present. We knew very little of the latent aspect of tuberculosis at that time. Little did we realize that infection occurred in childhood to so great an extent as we now know. When the newer methods of applying the test had been made known, however, and when they had been widely employed, it was found that a tuberculin reaction in itself only indicates that tuberculosis antibodies are present. They may be due to an active, a quiescent, and for a certain time after healing has occurred, to a healed lesion. When its results were compared with post-mortem evidence, it became apparent that the test produced a reaction in many individuals who had shown no evidence of suffering from active tuberculosis. This fact has caused a great deal of confusion and disappointment in the minds of those who previously were wont to place reliance in its diagnostic worth. This confusion has spurred investigators to renewed efforts to learn how to interpret properly the test to see if it cannot still be preserved as a method of great diagnostic worth.

I have already shown how our idea of what constitutes an early diagnosis has changed with each new refinement in diagnosis. Coincident with this increased diagnostic ability, the importance of the various aspects of the disease which had previously been unrecognized has increased, until at the present time our conception of tuberculosis as a disease is so different from what it once was that it calls for an entirely new consideration.

We are now attempting, with a fair degree of success, to recognize this disease in its incipiency, a condition which was not recognized previous to the tuberculin era. It seems prob-

able that the confusion which exists at the present time regarding the reliability of the tuberculin test will call for a closer study of it, and result in a better understanding of it and its true worth. I am convinced that much valuable information can be derived from a more accurate study and a more careful interpretation of the reactions which occur. It is quite probable that points of distinctly differential diagnostic importance between active, latent, and healed lesions may be obtained by such a study. The writer's observations on this point are encouraging (pages 33–37).

Some observers go so far as to discredit all forms of the tuberculin test when applied to adults; others confine their lack of confidence to certain forms of the test; while still others maintain that careful interpretation of any one of the cutaneous, subcutaneous, or conjunctival will give data upon which a fairly accurate diagnosis may be based in adults as well as children.

A very confusing observation is that a patient may react to one test and not to another given at the same time. This observation perplexes even the most ardent advocates of the test, and so far remains without a wholly satisfactory explanation. Fortunately, it occurs comparatively infrequently and affects the percentage of results very little. This difference in result may be in part due to technic, or it may be due to differences inherent in the various tests themselves; or it may be an individual matter, wholly dependent upon the patient. We do not know. But no matter how many of the tests are administered, if the patient reacts to any one of them it shows the presence of tuberculosis antibodies and should be taken as proof of the fact that he has been infected by tubercle bacilli at some previous time.

In order to appreciate the meaning of early diagnosis and the full value of tuberculin as a diagnostic agent, it is necessary to keep constantly before us the fact that nearly all people are infected with tuberculosis, and that a very large proportion of them suffer from active, though probably unrecognized, symptoms some time during their lives. It must be remembered that the one ninth or one seventh of the human race that die of tuberculosis is only a part of the entire number who show symptoms. A much larger proportion suffers from what is recognized as clinical tuberculosis, and a still much larger proportion suf-

fers now and then from symptoms which, though rarely recognized, are, nevertheless, due to activity in partially quiescent foci. It is probable that our diagnostic efforts in the future will trend toward recognizing these quiescent cases and putting them on the right way to a complete healing. In this the tuberculin test will be a great factor.

Latent Tuberculosis Dangerous.—An erroneous idea seems to have gained ground respecting the actual condition and relative danger of tuberculosis in the various stages of healing, quiescence, and activity. Of these, only a complete healing is safe. If, after the infection has occurred, the defensive forces of the body have been sufficiently raised to cause the bacilli to be destroyed, then no further harm can be expected from a focus. If, on the other hand, the focus should become latent and stop short of healing, with the bacilli shut up in the tissues, their toxins will now and then reach the circulation. While we cannot understand this as being pathologically healed, yet, as long as it remains in this condition, the patient will be safe. The patient cannot be considered as free from danger, for the bacilli are still there, ready to become active if favorable conditions arise. They are in free communication with the blood-stream, as is shown by the fact that their toxins are discharged now and then with the production of clinical symptoms—such as malaise, nervousness, rise in temperature after exertion, and variations in the opsonic index.

Active tuberculosis is fairly well understood; but even here, the advanced stage is far better recognized than the early. The signs and symptoms which accompany the early period of activity do not seem to be very thoroughly impressed upon the profession as yet. The important thing for clinicians to recognize is that latent tuberculosis is to the human organism what a bomb is to a building under which it has been placed. If the fuse is not lighted there will be no harm; if the quiescence or latency is not disturbed there will be no active symptoms. The duty, in the one case, however, is plain: remove the bomb. In the other it should be as plain, but owing to the difficulties of producing a healing in tuberculosis, our plan has been to let the disease alone in its quiescent condition and hope that it would remain so. With improved methods of immunization [illegible] treatment, however, we hope that it will not be long u

shall be able to cause a latent lesion to heal with comparative ease, and expend our energies on the disease while it is curable and while the patient can still be a useful member of society rather than deal with advanced tuberculosis where we are so often foiled in our attempts at cure and where the best result obtainable so often means only a limited usefulness.

The entire medical profession recognizes the necessity of operating on every case of appendicitis after the first recognizable attack has passed off, and yet the mortality from this disease without operation is less than fifteen per cent. Tuberculosis offers a mortality of about seventy-five per cent of clinical cases when untreated, and yet we hesitate to give our sanction for treating it during the quiescent stage. If proper practice for appendicitis, why not for tuberculosis? We cannot let the fact that the infection is so widely spread bias our scientific opinion.

With our present knowledge we, as clinicians, should demand that the clinical test of absolute quiescence or healing, exclusive of the tuberculin test, be that no signs or symptoms of toxemia develop even after severe bodily exertion, and that no active signs be found on auscultation. On physical examination, I would further suggest as a very valuable sign, the absence of spasm of the muscles covering the affected apex, particularly the trapezius, sternocleidomastoideus, and scaleni, as described by the author.[4] In one-sided lesions, an equally free expansion of the lungs on the two sides (except where there has been pleurisy at one base), showing that the reflex disturbance of the diaphragm caused by the acute inflammation has passed away, is also very important. I find, however, that many observers seem to fail in detecting the limitation of motion of the diaphragm while the disease is acute; and of course to them this sign will be of no value.

With the above requirements on clinical observation and physical examination and a careful study of the tuberculin test, I have arrived at the conclusion that a certain type of tuberculin reaction is very apt to go with activity, and a different type with quiescence.

Reactive Capacity of Patients Differ.—Preliminary to describing the differences noted in the character of the tuberculin reactions, it is necessary to mention several factors which enter

[4] Muscle Spasm and Degeneration, C. V. Mosby Co., 1912.

into the reactive capacity of patients. In the first place, the local reaction is the visible expression of the phenomena which occur when the union between the bacillary protein (tuberculin), and the antibodies, which are either fixed or circulating in the patient's blood, takes place. The amount of these antibodies varies according to the reacting powers of the patient and the amount of stimulating toxins set free from the tuberculous focus. We assume that these antibodies are found both attached to the cells and circulating in the blood. It is necessary to bear this in mind in order to understand the phenomena of tuberculosis immunity.

If the focus is not active, no toxins will be set free from the tuberculous focus, and consequently no new antibodies will be produced. Those which have been circulating free in the blood will disappear after a time, and only those fixed to the cells will remain.

If the disease is moderately active and the patient is in good general condition, the ideal condition for the existence of many free antibodies is present.

On the other hand, if the disease is very active, the patient's vitality is thereby lowered; and after a time his reactive powers are reduced, his power to form antibodies is lessened, and accordingly the free-circulating antibodies are reduced in amount.

The same lowering of the power to produce antibodies is noted when a moderately active lesion is present in an individual of low vitality.

Diagnostic Value of Nature of Reaction.—From this we can see that when a tuberculin test is given the reaction should vary considerably under different conditions of the patient and of the disease, as follows:

1. A healed lesion should show no reaction to any of the tests after the lapse of sufficient time for the excessive amount of antibodies (particularly free-circulating antibodies) which were required for the defense of the body, and which were called forth by the stimulation of the toxins produced during the state of activity, have passed away. Until such time the reaction should gradually lessen in strength.

In this connection I wish to repeat my conception that free-circulating receptors in quantities beyond the slightest amounts, in patients who are not treated with tuberculin, mean that an

active demand is made, or has been made immediately or shortly prior to the observation, for the protection of the organism against tubercle bacilli. When no extra demand is made, the receptors, for the most part, remain fixed to the cells; consequently a healed lesion should show no free receptors except for a period, the length of which we do not know, after healing has occurred.

2. A quiescent lesion should offer little opportunity for the formation of antibodies, because the specific stimulus is thrown into the circulation only in small amounts and infrequently, and therefore should show a weak reaction or no reaction, unless the test be given soon after toxins have escaped into the tissues; and if the patient is suffering from low vitality and is unable to respond in the production of antibodies, it might give no reaction at all and thus be erroneously interpreted as meaning no lesion or a healed one.

The cutaneous reaction in a partially quiescent lesion may be as marked as in a definitely active one, but it will take longer for the antibodies to gather at the point of inoculation in sufficient quantities to satisfy the tuberculin; hence the reaction is slower in manifesting itself. It may not reach its maximum until the second or third day.

3. A moderately active lesion in a person with good vitality should show a marked reaction to all tests; and in a person with low vitality, a moderate reaction, or it might be slight or even no reaction at all.

It is further characteristic of the cutaneous reaction in active lesions that it reaches its maximum early, usually before twenty-four hours from the inoculation. This is due to there being sufficient free receptors to satisfy the tuberculin quickly.

4. Advanced tuberculosis, whether slight or moderately active, may give no reaction or a marked reaction to all the tests, according to the vitality of the patient.

In patients of low vitality the tuberculin test is not so reliable, and we must not rely on the evidence adduced by it, especially if it is negative in character. In advanced tuberculosis the test is unreliable, but it is not necessary, as the diagnosis is easily made otherwise.

It can readily be seen that there is a good theoretical basis for the tests—particularly the cutaneous—being of value in dif-

ferentiating active from quiescent lesions, and also in determining the reactive capacity of the patient.

In an experience of sixteen years with the subcutaneous test I have been convinced that most of the cases, at least which have reacted to one large dose of tuberculin, 5, 7, or 10 milligrams, were cases of positively active tuberculosis as judged by the symptoms present. I have also found that I can interpret the results of the cutaneous test with a fair degree of accuracy, and base a fairly good opinion upon the activity or quiescence of the disease according to the nature of the reaction. This I shall discuss later (pages 33–37).

Wolff-Eisner maintains that a reaction to the conjunctival test means an active lesion, and gives a plausible explanation for the same. Others, however, fail to agree with him. I shall refer to these views again in describing the various tests.

Tuberculin Reaction May Be Negative Immediately Following an Initial Hemorrhage.—It is necessary to understand that a patient may fail to react to tuberculin, although he has had an unquestionable pulmonary hemorrhage, if the test be given at once or soon after the hemorrhage occurs. This, however, is only in a certain class of patients who expectorate a few mouthfuls of blood suddenly without warning or without previous symptoms of any kind. The hemorrhage is due to a sudden rupture of a tuberculous mass from a previous infection into a bronchus and injuring a vessel at the time it occurs. Under such circumstances the toxins have not been escaping into the blood-stream, and there has been no response on the part of the body cells in the production of antibodies; consequently, no tuberculin reaction occurs. If there is an extension of the disease at the time the bleeding occurs, or if the old process becomes active, the toxins will escape into the tissues, and an immunizing response will take place; and if the test be applied later, a reaction will occur. On the other hand, if the process ends with the expulsion of the mass and hemorrhage, and no extension occurs, a negative reaction will occur both immediately and later. I have seen several patients who, in spite of an unmistakable hemoptysis, did not react to the tuberculin test, when given at once after the hemorrhage, but who did react later. I have also seen several who failed to react both at once and later. The former had an activity started up at the time of the blood-

spitting; the latter were not disturbed in the least by the occurrence.

Interpretation of the Tuberculin Test.—The tuberculin test primarily is to determine whether or not tuberculosis antibodies are present. If any one of the tests are given and there results a positive reaction, it can be said with positiveness that either clinical or pathological tuberculosis is present, because a reaction to tuberculin is specific; that is, it is a reaction caused by the presence of immune bodies in the organism, which can only be produced by the body cells coming in contact with and responding to the stimulation of toxins produced by tubercle bacilli.

In those instances which have been reported where some other disease is supposed to have reacted to tuberculin, the error is most probably on the side of the observer rather than on the part of the test. If we judge of the character of the reaction and the time of its occurrence, especially when dealing with the cutaneous test, we are able to determine to a certain extent whether or not the tuberculous process which causes the reaction is active or quiescent. This, of course, is one of the important things that we are attempting to do in our clinical dealings with tuberculosis. While it is not recognized by observers generally, yet my personal experience indicates that we have a fairly accurate measure in the time and character of the reaction for basing an opinion of activity or quiescence.

There are many patients in whom it is important to make a diagnosis, who will give a negative reaction although tuberculosis is present. In individuals who are in fairly good physical condition, we can expect the tuberculin test to give reliable information. In those who are weakened, however, those who are cachectic, those who are suffering from an advanced tuberculous lesion, and those who are suffering from numerous infectious diseases, particularly measles and scarlet fever, our information is very unreliable. This makes it essential, if the test should be given during the course of any of the acute infectious diseases, for us to withhold our opinion and repeat the test again after the acute infection has passed away, and in those cases whose general health is undermined, we are forced to rely upon other measures for our diagnosis.

Neither does the tuberculin test give us any information as

to the location of a lesion, unless there is a focal reaction, which can only be expected when the subcutaneous test is employed. It is not sufficient for the examiner to find a lesion in the eye that is suspicious, and giving the patient a tuberculin test which proves to be positive, draw the conclusion that the patient is suffering from ocular tuberculosis. We all know that unfortunate misinterpretations such as this have occurred in the past. For example, we recall a kidney which was removed by a noted surgeon because the patient was suffering from some inflammatory condition of the kidney and reacted to the tuberculin test. Many other similarly mistaken diagnoses have come to the ears of most of us; for example, I recall a patient who was suffering from some obscure abdominal lesion. The physician gave a tuberculin test, and as he said, in order to make it sure, he gave the injection on the thigh near the abdomen in order to get as near the supposed lesion as possible. The injection resulted in a reaction. He therefore drew the conclusion that the patient was suffering from abdominal tuberculosis.

It should be regarded as established that the tuberculin test does not tell where the tuberculous lesion is located; so, while it gives valuable information, it still requires the same common sense and judgment that have been required heretofore in order to locate the lesion and make the diagnosis accurate. Although the tuberculin tests are not perfect and often fall short of giving us the exact information which we greatly desire, I should not be at all surprised if the future would show us that our technic and observations have been far more erroneous than the tests themselves, and that what we now look upon as inaccuracies inherent in the tests will eventually prove to be largely due to our own limited vision and erroneous interpretations.

CHAPTER II.

SUBCUTANEOUS TUBERCULIN TEST.

The subcutaneous tuberculin test was the only one known from 1890 until 1907, since which time the various other methods have been brought forth. While the failure of the medical profession to appreciate tuberculin, and to succeed in employing it as a therapeutic measure when it was first introduced, brought it into disfavor as a remedy to be employed in the treatment of tuberculosis, thus depriving those suffering from tuberculosis of its benefit for several years, its use as a diagnostic agent increased, and its value became more and more appreciated as time went by, so that it was fairly well established by the time the new tuberculin era was ushered in.

Original Fear of Test.—In spite of the recognized value of the test and in spite of the difficulties encountered by the profession in diagnosing tuberculosis by other methods, the fear of tuberculin was so great that in some quarters its employment was absolutely ruled out until within the last few years. There probably never has been a remedy so generally feared and so universally hated as tuberculin. The fact that the fear was unjustifiable did not make it any easier to overcome. It was based on a failure to employ it correctly at the time when it was first introduced, and on the harm resulting from this failure. The remedy was just as good then and just as free from danger when properly employed as it is now. While it has been difficult to find any one who could point to an instance of definite harm resulting from the application of the tuberculin test, at least, as applied by the method of gradual increase as it was developed after the profession had regained its composure, yet the profession was so impressed with the fact that there was danger of starting up activity in latent foci and causing the disease to spread that the test was forced to gain its friends against great odds. When we think of patients being submitted to an anesthetic and an exploratory incision with its attendant dangers

that a diagnosis may be made, and then think of the same profession that sanctions this withholding its sanction from the tuberculin test when a supposed harm resulting is the only evidence against it, we cannot help thinking that our conservatism is somewhat unfair to the tuberculous patient. But this is in keeping with the attitude of the profession toward the tuberculous patient throughout. We fail to make a diagnosis early; we fail to inform the patient of the nature of his trouble when the diagnosis has been made; we fail, as a rule, to suggest curative treatment until it is too late. Thus, the attitude of the medical profession toward the tuberculous patient has been one of delay, indefiniteness, and indecision throughout. The positive attitude, strange to say, has often been on the side of withholding measures of diagnostic, therapeutic, and preventive merit.

Tuberculin, like many other good things, has been a victim of hasty conclusions drawn from insufficient or wrong data. And as is natural, all of the bad things said about it were believed, while the favorable opinions were outweighed by the overpowering number of adverse criticisms.

Of the need of a test for early tuberculosis, such as the subcutaneous test purports to be, there can be no question. We think that we are still slow in the early recognition of this disease; yet our methods of examination, aside from the tuberculin test, have greatly improved since the early nineties. The credit for much of this advance, too, belongs to the greatly feared and maligned subcutaneous tuberculin test.

Tuberculin Reaction.—The value of the subcutaneous test depends upon the fact that when injected into the tissues of a person suffering from tuberculosis, in sufficient amounts, tuberculin produces certain definite phenomena; while the same dose, up to an established limit, produces no effect on one not suffering from tuberculosis. Koch, after careful experimentation, established the dose of tuberculin which may be administered to a healthy individual without producing symptoms as 10 milligrams. This, then, has been made the limit of dosage for the test. Any patient who reacts to 10 milligrams, or less, of Koch's old tuberculin, administered subcutaneously, is considered as suffering from tuberculosis; while anyone who does not is considered as free from tuberculous infection. This applies to early infections but not to gross lesions. There are also certain conditions under

which early infections fail to react, which will be noted elsewhere (page 28).

Koch gave to himself 250 milligrams at one dose. Although not tuberculous, he suffered from the same symptoms as those which accompany a tuberculin reaction (page 221), which are in turn the same as those resulting from a moderate dose of any other toxin. The symptoms passed off after a few days without harm resulting.

The reaction to the subcutaneous injection of tuberculin manifests itself in three ways: a local area of redness and induration may develop at the site of the injection; there may be a general reaction producing well-defined and characteristic clinical symptoms; and there may be a reaction in the focus of infection. Each of these types of reaction requires careful study.

Local Reaction.—The area of redness and induration which develops at the site of injection is akin to von Pirquet's cutaneous reaction and is due to the combination *in situ* of the tubercle protein (tuberculin) with the antibodies which are circulating in the blood. Aside from this specific reaction, there is an induration which appears at times at the site of injection when due cleanliness has not been carried out in making the injection. This is due to carrying bacteria from the skin into the tissues and can be avoided by careful technic.

The specific local reaction which appears when small test or therapeutic doses are being employed, as a rule, consists of nothing more than a slight induration accompanied by redness and a slight increase of the local temperature, which may at times be accompanied by a sensation of burning or itching, or soreness in the tissues. When large doses are given the phenomena are sometimes very marked and affect areas several centimeters in diameter. The condition rarely requires treatment; however, if it is painful, it may be relieved by either hot or cold applications. The cause of this reaction is most probably the local combination of the tuberculin and free-circulating antibodies.

General Reaction.—The general reaction which follows the subcutaneous injection of tuberculin as a test in tuberculosis is the one upon which the profession generally depends for the diagnosis. The phenomena accompanying it vary according to its severity. It was formerly considered that a rise of two de-

grees in temperature was necessary in order to indicate a positive tuberculin reaction. For one who is accustomed to using tuberculin this is not necessary, for there are other unmistakable symptoms which go with it, and which usually appear short of a temperature rise. The temperature caused by the tuberculin reaction (Fig. 1), as a rule, begins to rise some time between eight and sixteen hours after the injection is given, although it occasionally appears as early as three or four hours and it may be delayed as much as two or three days. The time between the injection and reaction is the period of incubation. Proteins do not react immediately. They always require a period of incubation. Unless it be a very severe reaction, the temperature

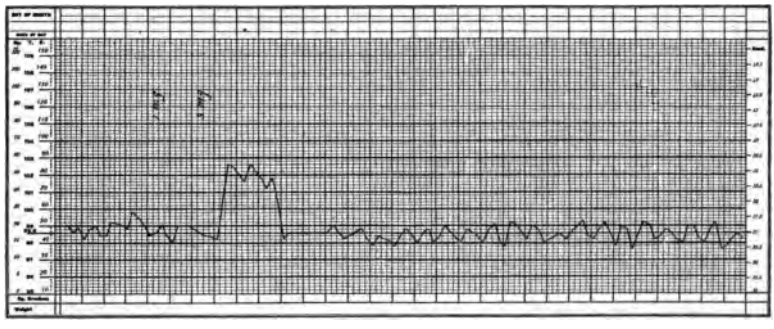


Fig. 1.—Illustrating tuberculin reaction in a case of early tuberculosis. It will be noted that three days previous to the reaction 1 milligram of Koch's Old Tuberculin was given, and on the day previous 3 milligrams were given with a very marked reaction resulting. It will also be noted that for several days following the reaction the temperature curve was decidedly steadied.

gradually returns to normal within 24 or 48 hours. Often with a slight temperature reaction, or even when there is no temperature reaction at all, the patient will show increased nervousness, malaise, a feeling of heaviness about the limbs, slight discomfort in the head or back amounting to almost an ache, or even actual pain. If, therefore, such a train of symptoms should occur after a test dose of tuberculin has been administered, it should be interpreted as a tuberculin reaction, even although no rise of temperature, or only a slight rise, has occurred; or, in case it was decided to give a further dose, it would be better to repeat the same dose that produced these symptoms rather than increase the dosage. If the reaction be stronger, the nervousness may be severe, the malaise be very much exaggerated, the feeling

of heaviness about the limbs be more marked, and the aching of the head and back be quite severe, resembling the toxic symptoms which occur in la grippe or acute tonsillitis. Sometimes vomiting, slight chilliness, or distinct chills are present. Such a severe reaction is nearly always accompanied by a marked rise in temperature.

Such a reaction is probably caused by the fact that there is an excess of toxins over the amount which can be cared for readily by the antibodies present.

Focal Reaction.—For those who are accustomed to using the test and accustomed to diagnosing tuberculosis, the focal reaction often gives valuable information. The focal reaction consists of a hyperemia or congestion which is produced in the tuberculous focus. If the disease is in the lungs, this sometimes causes an increase of cough, a feeling of constriction, a shortness of breath, an increase of mucus; and on physical examination, rales may be heard where they were not previously heard, or there may be an increase where there were few before. In the larynx, or any other visible focus, such as lupus or tuberculosis of the pharynx, this focal reaction shows itself as an increased redness. If the kidney is involved, we may have pain referred to that organ. (There seems to be considerable misinformation regarding the focal reaction as it occurs in the kidney. Resulting from a focal reaction in the kidney, there may be an increase of albumin and blood-cells in the urine. There may also be an increase in the number of tubercle bacilli, or, where no tubercle bacilli have been found previously, they may be found after a reaction. Pain may also be present, but it is not necessary for any or all of these to occur.) A focal reaction may occur and be unattended by any recognizable symptoms. Where the bladder is involved, we may find a frequency of micturition.

I must say that my own experience has not coincided with what seems to be written by other men regarding the frequency of pain in the area of involvement. I have not seen pain in the testicle, ovary, kidney, joints, bones, and glands as frequently as the literature would lead one to believe, but of course, where it does occur, it is very valuable as diagnostic evidence.

The focal reaction is probably due to the union of tuberculin and the antibodies in the focus of infection. It may occur short

of a general reaction. (The cause of these reactions is discussed more fully on pages 4, 37, and 70.)

Selection of Tuberculin for the Subcutaneous Test.—While any tuberculin might be used for the subcutaneous test, yet I think it is best to employ Koch's old tuberculin, because we know how to use it best. It is a fairly definitely settled fact, although disputed by some good observers, that if a patient does not react to 10 milligrams of this preparation we can safely say that he is not suffering from active tuberculosis. Of course, we must recognize that there is some degree of error even here, because different preparations of tuberculin differ somewhat in their power of producing reactions; but if we follow the rule of making 10 milligrams of old tuberculin our limit, we shall not go far wrong in our diagnostic results. Bovine tuberculin made after the same formula as Koch's old tuberculin can also be used, but I cannot think that it has any advantage; on the contrary, for general use as a test, I think it has disadvantages when compared with the human tuberculin. My experience in the use of human and bovine tuberculin would indicate to me that these two preparations differ. A reaction from bovine tuberculin is not so severe as a rule; and it comes on later than that produced by human tuberculin. Sometimes a patient will react to one and not the other, or to the two with different degrees of severity, but this might be accounted for in the same manner as the differences which occur in the same preparation of human tuberculin made from different cultures. A reaction to either should be considered positive.

Dilution of Tuberculin.—The dilution of tuberculin is simple. A great many fail to use it simply because they fear to undertake to make the dilutions. I think it is better, if one is only using it occasionally, to have the pharmacist make the dilutions; but if one is using it to any great extent, he had better learn to make them himself. Dilutions should be made fresh at the time of each injection, or at least every ten days. I do not think it wise to keep dilutions longer, although the original solution may be kept almost indefinitely, if tightly corked. Any solution, either original or the diluted, should be discarded if it contains a precipitate.

Method of Making Dilutions.—The only apparatus necessary to make the dilutions are a graduated pipette, or syring

two sterile bottles. The pipette or syringe should be graduated preferably in the metric system. It should be of small caliber because this reduces the percentage of error. Two dilutions of the original tuberculin should be made: one a 1:100; the other a 1:1000. As a diluent I use normal salt solution, plus two fifths of one per cent carbolic acid. In order to make the 1:100 dilution, 0.1 cubic centimeter of the original solution should be diluted with 9.9 cubic centimeters of the diluent. Of this solution 0.1 cubic centimeter equals 1 milligram (0.001 c. c.) of tuberculin, and a syringeful, or 1 cubic centimeter, equals 10 milligrams (0.01 c. c.) of tuberculin. To make the 1:1000 solution, 0.1 cubic centimeter of the 1:100 solution should be taken and diluted with 0.9 cubic centimeter of diluent. Of this dilution, 0.1 cubic centimeter equals 0.1 milligram (0.0001 c. c.) of tuberculin, and 1 cubic centimeter equals 1 milligram (0.001 c. c.) of tuberculin. These two dilutions are sufficient, because from them we can accurately measure the dosage that is used in diagnosis, the minimum dose usually being about 0.1 or 0.2 milligram, and the maximum dose being 10 milligrams.

Applicability of the Subcutaneous Tuberculin Test in Early Tuberculosis.—Where the disease can be diagnosticated by other methods, such as physical examination, clinical history, and examination of the sputum, the test need not be used. I have no fear, however, in the use of the test; yet I think it should be guarded from abuse and should only be used where the knowledge derived from it is essential in order to give the patient the benefit of early diagnosis. The fear of mobilizing bacilli and starting up activity in a latent focus can no longer be held as an argument against this test. There need be no fear of producing either harm or death by the proper use of the subcutaneous tuberculin test. These objections, if they were valid, could now be overcome without depriving the patient of the value of the tuberculin test, because we have the other methods of applying it. If, however, it were necessary to use the subcutaneous test, no one should hesitate, because there is no danger from the test itself and most of those conditions which have usually been given as contraindications should be discarded on the ground of the importance of the information to be derived. Especially is this true in regard to diseases of the heart and of the kidney, unless the lesion be very serious. Hemopty-

sis is a contraindication, and if spitting of blood has occurred within a few days, the test should be withheld at least for a week or ten days after the last trace of blood. In an initial hemoptysis reaction may not occur (page 13). In an early case, however, where the subcutaneous test would be necessary in order to determine the presence of tuberculosis, there would be little danger of a focal reaction producing a serious hemorrhage. It is only in advanced cases where we have an extensive lesion that we expect anything serious from hemoptysis. I think that any acute infection should be considered as a contraindication to the subcutaneous test, because there would be some question as to the cause of the rise of temperature under such circumstances; there would also be a question as to the cause of the malaise or other toxic symptoms which might accompany the general reaction.

So able a champion of tuberculin as Sahli has great fear of a focal reaction. In the third edition of "Tuberculin Treatment," translated into English, I find on page 85 that he says: "I consider the early diagnosis of tuberculosis of the greatest importance and am convinced of the value of tuberculin treatment, but am absolutely opposed to diagnostic tuberculin injections." In the theoretical part (p. 144) he says: "It will be seen that Wolff-Eisner has collected evidence that goes to prove that no definite conclusions can be drawn from either a negative or positive result for so-called diagnostic injections. Aside from this fact I consider the risk attending their use sufficient argument for their rejection. Indeed, how illogical it would be to advise the exposure of patients to the danger of overloading with toxins merely for diagnosis, for we have emphasized the fact that tuberculin treatment is only harmless when the greatest care is taken in dosage and all reactions avoided."

I can speak freely with reference to this attitude taken by Sahli because I have had an extended experience in the subcutaneous injection of tuberculin both for diagnosis and therapy. I have never seen the least harm result from the diagnostic injections, even though the temperature rose to 103°. It has long been my habit, however, not to require any definite rise of temperature, but being thoroughly conversant with the symptoms that go with a tuberculin reaction, the malaise, feeling of heaviness, aching, and increased nervousness, together with the focal

reaction which may at times be detected, I have usually been able to make my diagnosis short of the formerly demanded two-degree rise of temperature. Unless the injections are given in cases where they are unnecessary, where there are advanced active tuberculous lesions, I cannot see where the danger from a subcutaneous test lies; and as I have said elsewhere, if it were necessary to give the subcutaneous test in order to make a diagnosis in a disease so serious as tuberculosis, it should be used in spite of the supposed danger that attends it. It would certainly be as justifiable as the generally accepted exploratory incision in abdominal lesions. If taking the risk of making a lumbar puncture or giving an anesthetic for diagnosis is justifiable, I can see no reason for opposing the injection of tuberculin because there is a supposed possibility that it might do some harm in an infinitely small per cent of cases in which it would be used. Fortunately, the other forms of the tuberculin test make its employment unnecessary in the great majority of cases.

Healing Stimulated by Reaction.—The frequency with which patients who have been suffering from active tuberculosis improve, following a reaction produced for the purpose of diagnosis, will more than offset any supposed harm that might have resulted in other cases. Anyone who has had much experience in the employment of the subcutaneous test must have observed this.

What is Necessary Before Giving the Subcutaneous Test.—Preliminary to giving the tuberculin test, the patient should be examined most carefully, and other methods of determining the presence of the tuberculous lesion should be exhausted. A minute history of the patient should be taken, and the part supposed to be tuberculous should be thoroughly examined. If it is the chest, the supposed site of the lesion should be located so that it might be watched carefully for a focal reaction after the injections are given.

The patient should be given a reliable thermometer and a temperature chart and should be required to take his temperature every two hours for at least three days before the test injection is to be given. The patient should do the same during the time that he is making this preliminary temperature record as he is going to do after the test injection had been administered. It is not absolutely essential to confine patients in bed,

although it is the best method of handling them where this is practical; but if the patient is to be in bed after the test is given, he should be in bed during the three days that he is taking his temperature preceding the test. If he is going to give up his work after the test, he should do the same during the preliminary three days' test of temperature.

The temperature should be taken accurately. The thermometer should be held in the mouth sufficiently long to give it time to register, and the mouth should be held tightly closed while the thermometer is registering. Talking, or taking the thermometer out to look at it, or anything else which interferes with keeping the mouth closed, should be avoided. A one-minute thermometer should be held at least three minutes, better five. A two-minute should be held at least four; a three-minute should be held five, and a five-minute should be held ten. If the weather is cold, and the patient has been exposed to the cold air, the thermometer, no matter what its marked registering time, should be held ten minutes, for it requires at least ten minutes to warm up the mouth in cold weather after the patient has been out of doors. These precautions are absolutely essential if accuracy is to be obtained, and unless every detail is carried out it is useless to put reliance on the tuberculin test.

Rectal temperature is more accurate than that taken by mouth, and strictly speaking, it would be better if it were employed; but for esthetic reasons as well as for reasons of convenience, it is rarely employed in this country. If the precautions that I have mentioned for taking the mouth temperature are carefully followed, it will be sufficiently accurate.

The patient should be instructed not to take the temperature soon after drinking or eating. Cold or warm water or food will affect the temperature of the mouth for some time.

Technic of Administration.—The administration of the test does not differ in technic from that in the use of ordinary hypodermic remedies. The only essential is getting a measured dose of the tuberculin into the tissues, although the patient will appreciate it if the injection is given quickly and a sharp needle is used, for this makes the injection practically painless.

In this day of perfection in instruments the all-glass Leur syringe, or the Record, which has a glass barrel and solid-metal piston, is ideal (Fig. 25). Both of these can be sterilized thor-

oughly and quickly. A platino-iridium needle, while not essential, is very desirable, because it can be brought to white heat before and after each injection.

The choice of a site is of no consequence whatever, except for the fact that some places are more convenient than others, and less sensitive. I have used the interscapular region, the upper arm, the forearm, and the abdominal and lumbar regions; but I prefer the flexor surface of the forearm because it is convenient, and further, because it is easy to observe the local reaction in this region. I also prefer to give the dose subcutaneously, although deep muscular injections are equally effective.

There has been considerable discussion regarding the time of injection. I, personally, prefer to give the dose late at night —nine o'clock is a convenient time. The patient then goes to sleep, and by waking in the morning at five or six o'clock he can record his temperature at the earliest time that a reaction would usually be expected. The temperature should then be kept regularly every two hours during the day until at least three days after the last test injection, remembering that a reaction may occur two or three days after the injection has been given.

Dosage.—The question of dosage is an important one, although it might not seem so from the various methods in vogue. Koch suggested three doses: the first of 1 milligram, increased to 5 milligrams, and then finally 10 milligrams, the latter to be repeated in case of failure to react. There is a great deal to be said in favor of one large dose of 5, 7, or 10 milligrams; but owing to the great fear of marked reactions, which has prevailed among medical men since the early trial of tuberculin, most men have become more careful and seem to think that prudence, at least, demands a more cautious method; consequently the method of gradual dosage has almost entirely taken the place of the one large dose, even although accuracy is sacrificed by so doing. I, personally, have used both methods, and while I have never seen any harm come from injecting one large dose of tuberculin, and while I believe this method is the more accurate, yet I prefer the gradual method as being surrounded by greater caution.

In the method of repeated small dosage it is not impossible that in the reaction following the third or fourth dose we are obtaining a reaction of hypersensibility to the previously in-

jected protein instead of a reaction due to the immune bodies in the blood of the patient, resulting from an existing tuberculous focus. Wolff-Eisner thinks this a genuine objection to the method. Those who use this method, however, maintain that the non-tuberculous will only react after six or eight injections have been given, while the tuberculous react after the third or fourth.

My method depends entirely on conditions. I study my patient and gauge my dosage according to the earliness of the lesion, according to whether I consider there is much activity present or not, and according to the age and physical condition of the patient. If the lesion is early and inclined to be active, I give a smaller dose than in case it is more extensive or a lesion fairly quiescent. If the patient is reduced in vitality, I begin with a smaller dose than if the patient is strong. In a child I give a dose from one tenth to one half that of an adult. With the average adult my initial dose is 1 milligram. Two days later, if there is no reaction, I give 3 or 5 milligrams; three days later, in case of no reaction, I give 7 or 10 milligrams, according to conditions. If the patient is a child, or one whose vitality is lowered, I would generally begin with $\frac{1}{10}$, then 1, 3, and 5. While I realize that a patient might react to ten who does not react to seven, for the sake of safety I feel that caution is warranted. Some observers will maintain that my initial dose of 1 milligram is too large. In answer I will say that sixteen years' experience has not proved it to be so. Other sequence of dosage which has been followed is $\frac{2}{10}$, 1, 5, and finally 10 milligrams.

Many articles have appeared in the literature suggesting extremely small doses for diagnostic purposes. I must say, after a very extensive experience in the use of tuberculin, that I cannot believe that these small doses can be relied upon in diagnosis. I have not often seen a reaction occur on the injection of 1 milligram. While we must always bear in mind that there is such a thing as hypersensibility and that very small doses repeated for several days may produce it, yet I question the reliability of such a method, although it has been suggested by a careful observer, Löwenstein. He suggests that $^2/_{10}$ milligram be repeated four times within ten or twelve days. The French clinicians use very small doses, rarely larger than $\frac{1}{2}$ milligram. It would seem to me that little reliance could be placed on re-

sults thus obtained. Knowing what we do of the subject of hypersensibility to proteins, I am of the opinion that we must admit that the result obtained by one large dose is more reliable than that obtained by several injections.

Maximum Dose.—While, of course, as mentioned above, we must admit that there cannot be any maximum dose of tuberculin which will definitely determine between the tuberculous and non-tuberculous, yet we feel that the 10 milligrams has proved to be exceedingly accurate. No one who has had experience with tuberculin and tuberculous patients and has seen the variations in the reacting powers of patients and the variability of the same preparations of tuberculin made from bacilli grown under different circumstances would believe that any maximum dose could be absolute; at the same time, my experience indicates that 5 milligrams for a child, 5 or 7 for an adult who is reduced in vitality, and 10 for a strong adult can be relied upon and used to great advantage in diagnosis. I would strongly urge, however, that, in the face of positive clinical symptoms and definite physical findings and a failure to secure a reaction to even ten milligrams of tuberculin, the diagnosis of probable tuberculosis be made and the patient be treated as tuberculous. This course would be unquestioned in almost any other disease.

Tuberculous Patients May Not React.—In studying the tuberculin test, if we bear in mind that the test is not one for tuberculosis directly, but rather for the presence or absence of specific antibodies and specific hypersensibility, then we will understand the limitations of the test better and not be disappointed when one suffering from advanced tuberculosis, or one who is cachectic, does not react. A certain amount of reaction must occur whenever tuberculin is brought in contact with the tissues of one suffering from tuberculosis, whether the process be healed, latent, or active, whether early or far advanced, and whether the individual's resisting power is good or bad. This reaction may be imperceptible and not accompanied by those phenomena which we have learned to associate with a manifest reaction; nevertheless we must assume that a reaction occurs, which, although it may differ quantitatively, yet is qualitatively the same. The reaction may not be visible. It is the same as most of those resulting from the therapeutic doses of tuberculin which are administered.

CHAPTER III.

CUTANEOUS TUBERCULIN TEST.

Von Pirquet, in 1907, made the observation that when tuberculin is inoculated into the skin through an abrasion a reaction occurs at the point of inoculation. He explains this as being a reaction of hypersensibility and due to a condition which he has described as allergy, from *ergeia,* meaning reactivity, and *allos,* meaning altered. This conception is a very important one from the standpoint of understanding the tuberculin reaction and also from the standpoint of understanding the specific protection which develops in the body against repeated inoculations of tubercle bacilli.

Our conception is that, in the early years of life, tubercle bacilli are frequently taken into the bodies of nearly all children. The invasion is probably repulsed and the bacilli are destroyed in most instances, at first by the non-specific protective agencies of the body, later by specific antibodies which are found as a result of inoculation. Each time that bacilli enter the body there result from the inoculation certain phenomena. Resulting from their destruction, certain toxins are set free which sensitize the body cells, stimulate them to the formation of antibodies, and cause them to be on the lookout to ward off any further attacks of bacilli. From the time of the first inoculation we must consider, then, that the reactivity of the body is changed toward tubercle bacilli and its products in such a manner that, if they are again introduced into the tissues, they are at once seized upon by the specific antibodies, and a reaction occurs.

Allergy, or what I prefer to call by the more common name hypersensitiveness, to tuberculin or tubercle bacilli exists then only in bodies that have been previously inoculated with tuberculin or tubercle bacilli; therefore the allergic reaction to tubercle bacilli and their products is a specific one.

Von Pirquet's study of the local tuberculin reaction was the

result of a previous study made by him and Schick of serum disease and vaccina in 1903.

Importance of the Cutaneous Reaction.—The importance of the cutaneous reaction in its bearing upon the tuberculosis question has been great and far reaching because it has furnished us with a method for determining the presence or absence of tuberculosis, which is at the same time harmless and easy of application.

When von Pirquet's conception of allergy is fully understood it is at once seen that not only can this reaction be made a test for the presence of tuberculosis but that it also has special application in the detection of early tuberculosis and can be used in studying the time when infection takes place. In this one particular line of study it has completely changed our previously conceived notions.

Soon after its introduction many other forms of local reactions were brought forth. When it was discovered that a reaction occurs when tuberculin is brought in contact with an abrasion in the skin it was not long until the conjunctival reaction, the percutaneous, the needle-track reaction, the intradermal, and the modification of the cutaneous reaction by Lignières were brought forth. Aside from these, the various mucous membranes, those of the nose, urethra, vagina, and rectum, have been used simply to show that the reaction can occur anywhere in the body.

Infection Takes Place in Childhood.—Through the labors of pathologists we have been made to realize that tuberculous infection is very common and that most people have infections some time during their lives. We had been wont to consider, however, that the greatest danger of infection is in adult life; but after we began to apply these various modifications of the tuberculin test, and especially the cutaneous, conjunctival, and needle-track reactions, it became evident that infection occurs most commonly in childhood.

The work of von Pirquet, Hamburger, Ganghofner, and others soon demonstrated to us that tuberculous infection is extremely common during the early years of life. During the first few months there is almost no infection, but the amount increases as time goes on, so that by the time the fourteenth year is reached nearly all children harbor within their bodies a tuber-

culous focus. The importance of this knowledge is not yet fully appreciated, but it will probably eventually change the entire aspect of our warfare against tuberculosis and cause us to direct our preventive and curative measures to childhood instead of adult life, as they are today and hitherto have been.

Specificity of the Cutaneous Reaction.—With reference to the specificity of the cutaneous test, the reports of von Pirquet are very instructive.[1] He reported on about 1600 children on whom he made the cutaneous test. Of these, 200 died and went to post mortem. Of the 200 deaths, 68 had previously shown a positive reaction, and 66 of these showed macroscopical tubercles post mortem. In 2 cases the result was uncertain, but in 1 there were adhesions between the pleura and pericardium which were most probably of a tuberculous nature. When we consider that tuberculosis may be present in the lymph-glands and not even show microscopical changes and yet be able to produce the disease by inoculation, as has been done by Bartel,[2] and when we consider the ease with which a small focus could be overlooked, we can easily explain the failure in the one case. A negative reaction was found in 109, all of whom proved to be negative post mortem.

In several cases of fatal tuberculosis in older children the test, given only a few days before death, proved negative; in certain cases tested during an attack of the measles, the reaction was negative, although tuberculosis was present; and in a few other cases, where no definite reason for the failure could be given, the result was negative, although a lesion was present.

Since this report made by von Pirquet, further observation has shown that there are certain conditions under which tuberculosis, though present, will not react. It is probable that some of these conditions might have been present to account for the failure in the small per cent of cases mentioned here. The fact that tuberculosis was found in all but 2 of the 68 cases where the reaction occurred is quite remarkable and shows that when a reaction does occur we are justified in giving as our opinion that tuberculosis is positively present.

Conditions Under Which the Cutaneous Reaction Does Not Occur.—Molczanow,[3] in the Childrens' Clinic at Moscow, studied

[1] Report of International Tuberculosis Congress, Washington, 1908, vol. I, p. 458.
[2] Probleme der Tuberkulosefrage, Wein, 1909.
[3] Russky Wratsch, 1911, No. 43, p. 1637.

the cutaneous test with reference to various acute infectious diseases. His material consisted of 150 children. Of these, 42 were suffering from measles, 50 from scarlet fever, 50 from diphtheria, 2 from pseudocroup, 3 from varicella, 2 from mumps, and 1 from diplococcus sore throat. Of those suffering from measles, all failed to react as long as the eruption lasted. After the eruption disappeared, however, their reactive powers soon returned. In scarlet fever, in 85 per cent, the power to react to the cutaneous test was completely lost during the period of eruption, and in the other 15 per cent it was weakened. In diphtheria the power of reaction was completely lost only in 12½ per cent, but it was weakened in 50 per cent. The reaction which followed the injection of the antitoxic serum, as soon as it showed itself in a wide-spread eruption, also seemed to have an effect in reducing the strength of the tuberculin reaction. In varicella and diplococcus sore throat the reaction was unchanged.

The author agrees with Escherich in believing that this failure to react is due to the condition of the skin. Another explanation of the failure to react during the acute infectious diseases is that the specific immune bodies for tuberculosis, for some reason, are in abeyance during these infections. This would seem to be indicated by the frequency with which tuberculosis becomes active following them, especially measles. (A failure to react immediately following an initial hemoptysis is explained on page 13.)

Traumatic Reaction.—In a short time after the inoculation of tuberculin for the cutaneous test, both in the control and at the point of inoculation, a slight traumatic reaction occurs. The area about the abrasion becomes somewhat elevated and is surrounded by a zone of slight redness. The amount of disturbance at the point of control, as well as at the point of inoculation, depends upon the depth of the scarification and the particular reactivity of the patient's skin. Great differences are found in the reacting powers of different skins. This traumatic reaction usually disappears after a few hours; it shows either no inflammatory disturbance at all, or a very slight redness, the abrasion being covered with a small scab.

Positive Reaction.—If a positive reaction results from the inoculation, it will show itself in an increased inflammatory disturbance when compared with the site of the control (Frontis-

piece). The time and character of the reaction vary greatly. Both of these are influenced by many different conditions, some of which we do not wholly understand. They seem to be affected by:

1. The depth and method of making the scarification.
2. The strength of the tuberculin used in making the inoculation.
3. Whether the tuberculin is left in contact with the tissue for a long or short time.
4. The reactive powers of the patient.
5. The stage and character of the disease.

Very slight differences between the control and the point of inoculation should be discarded, although, strictly interpreted, any change in the nature of an inflammatory area at the point of inoculation, no matter how small, probably indicates a hypersensibility to bacillary protein and means the presence of a tuberculous focus in the body. When the reaction, however, emphasizes itself in any degree beyond this very slight change, it is unquestionably positive.

Negative Reaction.—If the reaction is negative, there should be no difference between the control and the point of inoculation. Von Pirquet recommended that those who are not familiar with the use of the test disregard any reaction which is less than five millimeters in diameter, or at least to consider this as doubtful; and further recommended that, in all cases where such reaction did occur, the patient be given a second test. I have always been in the habit, in such cases, of using some other test, either the intradermal or subcutaneous.

Interpretation of the Reaction.—When it comes to the interpretation of the reaction, unfortunately there is a great difference of opinion among medical men. It seems to be generally believed that the cutaneous reaction in an adult means nothing except the presence of tuberculosis, either healed, latent, or quiescent. If this is true, it can readily be seen that the test is of no particular value, because of the great frequency of tuberculous infection in the human family. If, on the other hand, there is a difference in the reaction, as it manifests itself in the presence of healed, latent, and active lesions, then this test will give us something that is invaluable in diagnosis.

The writer has been endeavoring, since he first began the use

of the skin reaction, to determine any difference that might exist in the reaction produced by these various conditions and believes that there is considerable difference to be noted under these various circumstances.

According to our present ideas that the frank active lesion is the only one to be treated in tuberculosis, it is very important that we have some method whereby we can differentiate active, latent, and healed lesions.

For a considerable period of time I have been observing the time and character of reaction in my tuberculous patients, and comparing it with my opinion of the case as formed from clinical history and physical examination, including the presence or absence of muscle spasm or degeneration.

The great difficulty in this grows out of the natural differences inherent in examining and giving opinions. Different men may examine the same patient and honestly differ as to whether or not activity is present.

The method which I followed was to take first a careful clinical history to see whether or not there was anything in the history which would indicate either an active or quiescent lesion; then make a thorough physical examination and note whether or not there were signs elicited in this manner which would point to either an active or quiescent lesion. Then I noted carefully the condition of the muscles, especially the sternocleidomastoidei, scaleni, trapezei, pectorales, and rhomboidei, to see whether or not they were normal or in a state of spasm, or whether they had undergone degeneration. Then I noted any diminution in the motion of the diaphragm as shown in a limitation of motion of the side of the chest, which might point to a disturbance in its function, due to reflex nerve irritation.

If I found in the clinical history something that was suspicious of activity and this was confirmed by the usual physical examination, and at the same time I found the muscles of the neck or chest in spasm, and the same condition suggested as to the diaphragm by the fact that its motion was limited, then I considered this case as one of activity. If, on the other hand, there were no symptoms of activity present in the clinical history, but the patient showed definitely that in the past such had been the case; and upon physical examination, instead of finding changes that indicated activity, I found evidence of an old lesion; and

then upon examination of the muscles I found that, instead of their being in spasm, they were degenerated, I considered this indicative of a latent or healed lesion.

Between a frank activity and an absolute latency there is a wide breach, but we often find patients whom it is difficult to classify either as latent or active. These are borderline cases and are the ones that are most difficult to diagnose.

After examining my cases in this careful manner I wrote down on the chart my opinion as to whether the case was active, quiescent, or whether it was on the borderline, neither very active nor wholly quiescent. I then gave the patient a cutaneous tuberculin test and observed the time and character of the reaction.

The character of the reaction, as mentioned above, depends very much upon the vitality of the patient, and his physical condition. In patients of good physique, but who have not been suffering from any severe disease which would produce rapid loss, but who came to consult me as to whether or not they might have a lesion, I found that, in nearly all instances where I had given an opinion of a positive active lesion based on clinical history and physical findings, there was a uniformity in the tuberculin reaction. It usually came on early, manifesting itself even as early as six hours in some cases. In most cases, however, where it was given in the afternoon, the reaction would be found the next morning on the patient's awakening. This would increase in severity during the day, reaching its maximum before or about the end of twenty-four hours. It would remain at its height for a short time and then gradually disappear. Aside from the reaction coming on soon in these early active cases, it was usually well marked. In those patients where I had given an opinion that there was a latent lesion I usually found that, while the reaction might be in evidence the following morning and keep slowly increasing during the first twenty-four hours, it would probably not reach its maximum until the second day and in some instances even the third. The reaction in these cases was usually also quite marked, but the principal thing that I noticed was that it did not come on so rapidly. In the borderline cases we had variations between these two reactions. A reaction might come on early but keep increasing after the first twenty-four hours. It was, as a rule, also a marked

reaction. When a case was practically healed, when we could find no evidence of anything but an old lesion, with no clinical symptoms and nothing to indicate activity, as a rule we had a very slight reaction on the day following the inoculation. There was usually a slight redness about the inoculation which rarely increased to any extent.

The following table, taken from a report made by the writer before the Los Angeles County Medical Association, November 21, 1912, shows a remarkable degree of harmony between the diagnosis in pulmonary lesions based upon a comparison of the results of: first, clinical history; second, physical examination; third, condition of the neck and chest muscles; and fourth, time and character of the von Pirquet reaction. The report is based on the careful examination of forty-four patients in whom early pulmonary tuberculosis was suspected.

No. Patients	Clinical History			Physical Examination			Muscle Spasm			von Pirquet Test		
	positive	negative	doubtful	positive	negative	doubtful	positive	negative	slightly positive	maximum before 24 hrs.	maximum after 24 hrs.	negative
2		2			2			2			2	
5		5			5			5				5
19	19			19			19			19		
9			9			9			9		9	
5	5			5			5				5	
2	2			2			2					2
2		2			2				2		2	
44	26	9	9	26	9	9	26	7	11	19	18	7

The fact that two cases show no pulmonary involvement would exclude them in making up our percentages, leaving forty-two patients to base our observations upon.

It will thus be seen that the clinical history, physical examination, condition of the muscles, and von Pirquet test, taking the twenty-four-hour limit as indicative of activity, agree in 76.2 per cent, giving a percentage of difference of 23.8.

The clinical history, physical examination, and von Pirquet test, based on the twenty-four-hour limit, agree in 78.6 per cent, giving a difference of 21.4 per cent.

The clinical history, physical examination, and the condition

of the muscles agree in 92.9 per cent, giving a difference of 7.1 per cent.

From these statistics, which I admit do not include so large a number of patients as is desirable, we cannot help observing the remarkable agreement in the diagnosis based on the various methods of obtaining data. Where we found the clinical history and physical examination indicative of activity we also found in nearly all instances a spasm of the muscles, and almost invariably a positive von Pirquet reaction, reaching its maximum within the first twenty-four hours. Where we found a negative clinical history and negative signs on physical examination, we almost invariably found no spasm of the muscles and a negative von Pirquet reaction. Where the clinical history showed that the case was only occasionally active and where the signs on physical examination made us feel that the disease was at least partially quiescent, we almost invariably found only a slight spasm of the muscles, and the von Pirquet test reached its maximum after twenty-four hours. It is possible that the twenty-four-hour limit is not the correct one to differentiate between active and quiescent lesions; but yet, as my cases will show, it was correct in the great majority of instances. It makes me at least feel that a von Pirquet test which comes on, reaching its maximum within or about twenty-four hours from the time the inoculation was given, is indicative of an active tuberculous process.

A percentage of error of only 23.8 between a thorough clinical history, physical examination, observation of the muscles, and the von Pirquet test, based on the time of reaction, certainly gives us a good working principle. If these results can be confirmed by others, the von Pirquet test may yet be saved to the profession as a means of differentiating between active and quiescent lesions.

In patients who are not in good physical condition, as a rule, we find that these reactions are modified. They may fail to appear entirely, or the reaction may be very slight and yet the lesion be active. These observations are in accordance with von Pirquet's opinion that a late reaction—that is, one coming on after twenty-four hours—is particularly caused by those cases which are clinically unsuspected.

Theoretical Grounds for Cutaneous Tuberculin Test Differentiating Between Active and Quiescent Tuberculosis.—In our idea of the cause of the reaction (pages 4, 70) we have a good theo-

retical basis for these clinical observations. We assume that the local cutaneous reaction is due to the union between the tuberculin and the antibodies, which, circulating in the body fluids, collect at the point of inoculation. The number of antibodies depends a great deal upon the reacting powers of the patient; therefore we expect them to be found in greater amounts in patients who are in good physical condition than in those who are physically weakened. They also depend upon the character of the lesion. From an active lesion the specific toxins are being poured out more or less constantly. They stimulate the body cells, which, in turn, produce antibodies. Where the lesion is latent, however, but not wholly healed, the toxins are not poured out so regularly or in such large quantities. Only now and then do they escape into the blood-stream. Consequently, the patient suffering from a latent lesion is not subjected to so frequent or so great stimulation of toxins as one suffering from an active one; so does not react with the formation of so many antibodies as one who has an active lesion. This shows itself in the character of the reaction. When the lesion is active, the antibodies circulate freely in the blood and gather quickly at the point of inoculation, thus producing an early reaction. They are also found in sufficient numbers to combine freely with the tuberculin at the point of inoculation; consequently a marked reaction results.

In the case of latent lesions the antibodies found in the tissues are fewer in number, but they may begin to gather at the point of inoculation equally soon, thus causing the reaction to begin as early as in active lesions; yet it takes longer for them to gather in large numbers; consequently the full reaction—that is, the reaction which comes from satisfying all the tuberculin with antibodies—is delayed. The result is that, while the reaction may come on as early as in the active case, yet it will keep increasing as time goes on, taking a much longer time to reach the height of the reaction, assuming that the reaction keeps increasing until sufficient antibodies are present to combine with the toxin (tuberculin) introduced.

In the case of a healed lesion we would expect that finally, after the toxins ceased escaping from the focus of infection, antibodies would cease to be produced; therefore the healed lesion should not react. For a time, however, after healing has

occurred—that is, as long as antibodies circulate in the tissues —we would expect some reaction to occur. Just how long this lasts we do not know, although I have frequently given the test to patients who had previously had definite tuberculous lesions which had apparently healed, and found no reactions, or slight reactions, to follow the inoculation.

It is not necessary to admit, however, that, when a patient fails to react, his protective immunity has disappeared. In this connection the idea of Wassermann and Bruck comes to our rescue. They suggest that the receptors in tuberculosis are sometimes anchored to the cells and sometimes free in the body fluids. As long as they are free they can gather at the point of inoculation and cause a local reaction. When anchored they are no longer circulating in the body fluids, and immunity might still be present and reaction not occur. Free-circulating receptors are formed in greatest abundance when the body needs the greatest protection, that is, when the disease is active.

To illustrate my meaning better, we might liken the specific immune bodies to the national army; the fixed receptors to the standing army; the circulating receptors to the national guard. Under normal conditions the standing army (fixed receptors) offers sufficient protection, but let a condition arise wherein the nation (body) is especially endangered and the national guard (circulating receptors) is called into service to offer additional protection.

There is some question whether the child is born with specific immune bodies. It is possible that the first bacilli that enter the body may be destroyed by non-specific antibodies; but after bacilli have once gained entrance to the body, its protective powers are called upon, and it organizes its defense. While the infection is occurring and being warded off, it organizes its protective army of fixed receptors (standing army) and circulating receptors (national guard), which keep in action as long as necessity demands. If the infection is overcome, the protection is left to the fixed receptors (standing army), and the circulating receptors (national guard) disappear from the bloodstream, not to be called out again unless the body should again be threatened by the tubercle bacilli and its toxins.

Whenever we find circulating receptors present, we know that the body has been attacked and that it is on the defensive.

When they have disappeared from the circulation we know that the danger has passed and that no recent attack has been made. The interesting thing for us to know is one that we cannot as yet determine, and that is the length of time after the conflict has ended when the body considers it safe to withdraw her free receptors from service. Could we know this, we would have data of unquestioned value in differentiating between active and inactive lesions.

If a latent lesion does give a delayed reaction, as my clinical experience seems to indicate, and as we would expect theoretically; and if an active lesion gives an early reaction, as my clinical experience indicates, and as we would expect theoretically, then we must attach a very definite value to this test, beyond that of determining the presence or absence of tuberculosis. We must ascribe to it a value in differentiating between active and inactive tuberculosis.

In dealing with borderline cases, those which would be neither markedly active nor wholly quiescent, our attitude as far as therapy is concerned should be definite. Tuberculosis which is not wholly latent must be considered as active; so, if there should be clinical history and physical findings indicative of activity, though it be ever so slight and though it might be present at irregular intervals and not constant, if the patient should show a tuberculin reaction which would indicate that the disease was not wholly quiescent, then we should treat this case as an active lesion. While this opinion may be considered extreme, I am positive that it is justice to the patient and justice to the medical profession to consider it so. In dealing with a disease so grave as tuberculosis, let us throw our opinion on the side of safety, especially when we have signs and symptoms which uphold us in so doing. This course is also in line with the best treatment of other diseases.

The Prognostic Importance of the Cutaneous Test.—From the above discussion it can readily be seen that information of diagnostic importance can be obtained from the character of the tuberculin test. With a given lesion the prognosis should depend upon what we call the patient's resisting power, which means upon the ability of the patient to react and form protective antibodies. All else being equal, the more freely the patient produces antibodies, the better his chances of cure;

therefore, if we make the cutaneous test in a given way in a number of individuals suffering from active tuberculosis, we would be safe in drawing the conclusion that those patients who react promptly with a marked reaction have a better chance of cure than those who react feebly. Wolff-Eisner has insisted upon the prognostic importance of the cutaneous test, although he does not believe so much in its diagnostic importance. I personally believe, however, that it has both diagnostic and prognostic values.

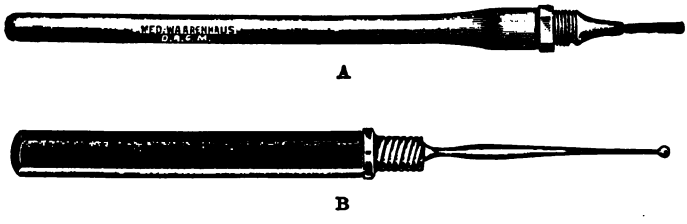
In considering the prognostic value of a tuberculin reaction, we must not put too much reliance upon it. We should not feel that a marked reaction means that the patient is sure of a cure, or that a feeble reaction means an altogether bad prognosis, because we can often change these reactions by changing the physical condition of the patient. A prognosis is a matter of too great importance to base entirely on a tuberculin reaction. In this connection we must also bear in mind that a patient may possess a high degree of immunity, as shown by all our known laboratory reactions, and yet the physical conditions surrounding the focus of infection be such as to make healing impossible.

Technic.—The technic of the cutaneous test is very simple, and yet oftentimes erroneous results are obtained by considering it so simple that sufficient attention is not given to detail. The test may be given by any instrument or implement which will produce an abrasion of the skin, but if we are making our tests to be compared with certain standards or for comparative observation, we should always make the test in about the same way. The same instrument, the same technic, as far as cleansing the skin is concerned, the same method of applying the tuberculin and making the abrasion, the same depth and same diameter of the abrasion should be used. It is only by observing these precautions that comparative results can be obtained. In making the abrasion for the control, great care should be exercised that the scarifier has been thoroughly washed from all remains of tuberculin. It should be washed in water. Alcohol will precipitate the tuberculin on the instrument and cause a reaction in the control abrasion. The tuberculin should be left in contact with the abraded surface for several minutes so that it may have an opportunity to enter the lymph-channels. Often the

sleeve is put down too soon, and the tuberculin is wiped away before it has had time to enter the tissues sufficiently.

While it is probably best to cover the point of inoculation with gauze in order to keep out infection, yet I have never seen any harmful result follow leaving it unprotected. Another very important reason for keeping it covered is to prevent the sleeve from wiping away the tuberculin. The skin may be cleansed with soap and water, or, what is better, alcohol or ether. The tuberculin, however, should not be dropped on the skin until it is dry.

The small needle designed by von Pirquet (Fig. 2) cannot be improved upon. It consists of a small cutting surface in the end of a handle, which is held firmly in the hand, the cutting surface being placed upon the skin of the arm and then the



A

B

Fig. 2.—A, Illustrating a von Pirquet scarifier; B, Illustrating scarifier made by H. M. Alexander & Company, of Marietta, Pa.

needle turned so as to cut through the cutaneous tissues without drawing blood. It is desirable to open only the lymph-spaces.[1] The needle should be made of steel, and disinfected carefully after each inoculation, or better, of platinum, when it can be brought to a white heat after each inoculation by holding it in a flame. It is best to make the skin taut by encircling the arm with the left hand and drawing the point of inoculation firmly between the finger and thumb (as shown in Fig. 3), while the inoculation is made with the instrument in the other hand. The drop of tuberculin should always be put on the arm, and the abrasion be made through the drop. In this way the scarifier brings the tuberculin in close contact with the lymph-spaces, whereas, if the abrasion is first made and then the tuberculin put on, the results are not quite so certain.

[1] A very convenient modification of this needle can be obtained from the H. M. Alexander Company, Marietta, Pa., the price of which is fifty cents.

Tuberculin Used.—For making the test Koch's old tuberculin is used. For comparative results it is very important that the same strength of tuberculin be always employed. I personally have tried dilutions of 10, 25, and 50 per cent, as well as undiluted tuberculin. It is impossible to compare the character of the reaction that results from a 10, 25, or 50 per cent dilution with that of the pure tuberculin; so I think it is extremely important to bear this in mind. After trying these various dilu-

Fig. 3.—Illustrating method of making cutaneous tuberculin test. The skin is drawn taut by the thumb and first finger of the left hand encircling the arm while the scarifier is used by the right hand.

tions I have finally discarded all except the undiluted tuberculin in the case of adults. In children I use either undiluted or 50 per cent.

It makes little difference in active cases whether weak or strong dilutions are employed, so that the results are interpreted properly. The strength of a reaction from a 10 per cent dilution, however, must not be compared with that of a 25 per cent, or undiluted tuberculin; but only with other reactions produced by dilutions of 10-per cent strength. The same is true of other dilutions. Comparative observations such as I am suggesting

can only be made by comparing reactions obtained from the same dilutions of tuberculin, the inoculations being made after the same technic. My personal results are from undiluted tuberculin. An experienced observer may use almost any dilution that he desires, but I believe that anyone who uses the test only occasionally should follow the rules which have been found to give the best results.

The test may be made anywhere on the body, but for convenience I think the forearm or upper arm is best. The control abrasion is not absolutely essential for one who is thoroughly conversant with the test, but should always be used by those who have little experience. I, personally, nearly always make a control abrasion, regardless of my wide experience.

Dilutions may be made by a normal salt solution, which contains ½ per cent of carbolic acid for preserving it. By the use of the concentrated tuberculin there is much less need of repeating the test.

CHAPTER IV.

PERCUTANEOUS TUBERCULIN TEST.

The test which is usually known as the Moro test consists of mixing Koch's old tuberculin and lanolin in equal parts, thus making an ointment which is rubbed on the skin. Of this, an amount equal to a pea in size is used in making the test. This may be rubbed into the skin at any point on the body, although, realizing the differences in the thickness of the skin in different parts of the body, it seems best to use some portion of the skin which is protected, such as that found on the abdomen. Moro recommended that the portion of the abdominal wall immediately beneath the ensiform cartilage, or the skin covering the chest, be used. The tuberculin should be rubbed into the skin by a finger protected by a rubber cot, the rubbing to continue for a minute or more. The protection of the finger of the one who rubs in the ointment is essential. Otherwise, in case he were tuberculous, he might absorb enough to produce a reaction.

Character of the Reaction.—The reaction usually occurs in from twenty-four to forty-eight hours after the inoculation has taken place and shows as a number of small red spots (Frontispiece). When the reaction is severe these spots are many in number and often appear like small nodules. They last for several days and when severe are accompanied by itching. When the regularly prescribed amount of tuberculin is used no constitutional symptoms appear. However, if a larger amount were used, it would be possible for a focal reaction to occur.

Carl Spengler has shown that definite tuberculin reaction may be produced by rubbing tuberculin into the skin. The Moro test could be used wherever the cutaneous test is employed, but personally I do not think that it is as reliable, and I further think it lacks the precision which comes in judging the nature of the reaction. There is such a difference between the thickness and absorbing power of different skins that there must be an element of uncertainty which does not hold in the cutaneous test.

Many prefer it because of its simplicity, and especially in children because the child is not frightened, as it is very apt to be by an instrument even so small as the scarifier of von Pirquet. I cannot think that it will remain a commonly applied test because of the uncertainty connected with it.

While one is fairly safe in saying that a person of good physique who does not react to the cutaneous test is free from tuberculosis, it would be wrong to draw the same conclusion in case one does not react to the Moro test. A negative Moro test in such an individual gives absolutely no information. A negative cutaneous test, on the other hand, gives very valuable information. The former is probably due to an error in technic; while the latter is probably due to the absence of antibodies.

Test of Lignières.—This consists in shaving the skin and rubbing into it five or six drops of undiluted tuberculin, and needs only to be mentioned. It has the same objections as the Moro test, without having as much to recommend it.

CHAPTER V.

CONJUNCTIVAL TUBERCULIN TEST.

Von Pirquet announced his cutaneous test in 1907. At the same time that he read his paper before the Berliner medizinische Gesellschaft on May 15, 1907, Wolff-Eisner announced his discovery of the conjunctival reaction. Calmette, as an independent observer, also announced the conjunctival test a few weeks later, June 17, 1907. While both of these observers deserve credit, inasmuch as their work was done independently, it would seem but fair to give Wolff-Eisner full credit for priority in the discovery.

Technic.—The technic of the conjunctival test is very simple. It consists in bringing a few drops of the dilute solution of tuberculin in contact with the conjunctiva and holding it there sufficiently long to guarantee that it will not be washed away by the secretion from the lacrymal glands. To insure this, the lower eyelid is drawn down, the drop instilled, and the lid held for a moment that the tuberculin may come in thorough contact with the mucous membrane. Then the head should be thrown back and held in that position for a moment to further insure the retention of the tuberculin.

Solution Used.—The preparation used in the conjunctival test by Wolff-Eisner is also Koch's old tuberculin. This should be diluted with normal salt solution, so as to make dilutions of 1 and 2 per cent strength. One or two drops of the 1 per cent is instilled into one eye. If no reaction occurs, later a 2 per cent should be instilled into the other eye. Wolff-Eisner experimented with many different dilutions, even as high as 10 per cent, but finally came to the conclusion that 1 per cent is sufficiently strong. The dilutions for the test should be made fresh at least once a week. It would be better to make them fresh every day. Baldwin[1] has suggested a uniform method for making this test.

[1] *Journal Amer. Med. Ass'n*, vol. LII.

than the cutaneous in determining active tuberculosis. While others disagree with him, his theory is plausible and must be given due consideration because of the great amount of study he has given the question of tuberculin in diagnosis. His reason for believing that those cases which react to the conjunctival test are active, while those that do not are quiescent, is based upon the fact that tuberculin when instilled into the conjunctival sac is either quickly absorbed or it is washed away. Unless there are great numbers of antibodies present in the circulating medium, the tuberculin would enter the tissues and be carried away before it would have an opportunity to combine with the specific receptors and produce a local reaction, in contrast to the cutaneous test where the tuberculin remains in the tissues until the antibodies gather, even if it takes several days; consequently, if there are many free receptors, as there are in active tuberculosis, we would expect a reaction; while, if there are few, as we would expect in less active or quiescent tuberculosis, we would not expect a reaction, for the tuberculin would be carried away into the circulating medium before the antibodies could gather in the mucous membrane to combine with the tuberculin.

Specificity of the Conjunctival Test.—Many have attempted to show that the conjunctival tuberculin reaction is not specific, the same as they have the other reactions. Their arguments, as a rule, however, are inconclusive. If they depend upon clinical examination, of course, it is worthless and falls without examination. If the opinion depends on the post-mortem evidence, then, of course, it is to be given more consideration; but at the same time, it is safe to ascribe it to unsuccessful search rather than to the absence of tuberculous foci. As previously mentioned, a tuberculin reaction means the presence of specific tubercle antibodies and a specific hypersensitiveness to tubercle protein, which in turn means the presence of a tuberculous infection.

than the cutaneous in determining active tuberculosis. While others disagree with him, his theory is plausible and must be given due consideration because of the great amount of study he has given the question of tuberculin in diagnosis. His reason for believing that those cases which react to the conjunctival test are active, while those that do not are quiescent, is based upon the fact that tuberculin when instilled into the conjunctival sac is either quickly absorbed or it is washed away. Unless there are great numbers of antibodies present in the circulating medium, the tuberculin would enter the tissues and be carried away before it would have an opportunity to combine with the specific receptors and produce a local reaction, in contrast to the cutaneous test where the tuberculin remains in the tissues until the antibodies gather, even if it takes several days; consequently, if there are many free receptors, as there are in active tuberculosis, we would expect a reaction; while, if there are few, as we would expect in less active or quiescent tuberculosis, we would not expect a reaction, for the tuberculin would be carried away into the circulating medium before the antibodies could gather in the mucous membrane to combine with the tuberculin.

Specificity of the Conjunctival Test.—Many have attempted to show that the conjunctival tuberculin reaction is not specific, the same as they have the other reactions. Their arguments, as a rule, however, are inconclusive. If they depend upon clinical examination, of course, it is worthless and falls without examination. If the opinion depends on the post-mortem evidence, then, of course, it is to be given more consideration; but at the same time, it is safe to ascribe it to unsuccessful search rather than to the absence of tuberculous foci. As previously mentioned, a tuberculin reaction means the presence of specific tubercle antibodies and a specific hypersensitiveness to tubercle protein, which in turn means the presence of a tuberculous infection.

CHAPTER VI.

TUBERCULIN IN THE TREATMENT OF TUBERCULOSIS.

Tuberculin as a Therapeutic Measure Well Established.—Tuberculin as a therapeutic measure is so well established today that when a clinician fails to obtain results by its employment he must consider that there is some error in his technic or his observation rather than believe that the remedy is at fault. I realize the fact that the opinion of the profession is not unani- in its endorsement of tuberculin, but this is nothing un-. The opinion of the medical profession is unanimous on few questions. The fact that many good observers, who studied tuberculosis carefully and who are devoting their ies to its cure, have been able to obtain good results from is sufficient to establish its value. The fact that other s, some of whom are equally interested in the cure of sis, have not been able to secure good results should be on as a personal matter rather than an argument remedy.

n not a Poison.—Tuberculin is not a poison. It can into a healthy man in large doses without producing l results. Toxic symptoms appear only when a focus exists, or when the dose is very large.

a very common belief on the part of laymen, as well nysicians, that tuberculin is some foreign poison en- raneous to the disease, tuberculosis, and upon this ny oppose its administration. Such is not true. Pre- any discussion on the subject of tuberculin therapy, e understood that tuberculin is nothing new to the patient. It is the same bacillary protein that is given s own focus of infection and the same protein which for the production of immunity; and without which, cure ever occurs in tuberculosis. Tuberculin is there- new poison that is being injected into the patient om tuberculosis, but it is the specific protein produced

on artificial media without the body by the same tubercle bacilli as are producing it within the body. Every patient who has tuberculosis treats himself with tuberculin as long as the disease is active. The only excuse for the use of tuberculin artificially is that we have found it to have immunizing and healing properties and have determined by clinical observation that we are able to hasten cure and make it more certain and more permanent by its employment.

Tuberculin Misunderstood.—Probably there never has been a remedy brought forth that has been received with such great expectations as tuberculin. Had it succeeded in meeting these expectations, it would have been adopted at once; but the fact that those who were willing to accept it were disappointed has made its later acceptance very much more difficult. Tuberculin therapy is commensurate with the therapy of tuberculosis, for no man can use tuberculin to the best advantage without understanding the entire treatment of tuberculosis.

Much of the misunderstanding which has come about with reference to tuberculin as a therapeutic measure has been due to the fact that men have undertaken to administer it who know nothing about the remedy and very little about the disease. They do not know what it is expected to do and have blamed it for their own misjudgment and mistakes. Tuberculin is not a perfect remedy. It will not cure all cases of tuberculosis. It will not do all the things that physicians have expected it to do; but if it will do the things for which it is specifically intended, it is vindicated in therapeutics. That it will not do all the things that are imposed upon it should not be counted against it, but against those who demand the impossible. In my book on pulmonary tuberculosis,[1] when discussing this point, I said:

> These remedies will not remove fibroid tissue nor will they restore tissue lost by ulceration. They cannot restore shrunken lungs nor can they replace distorted and damaged hearts. They cannot destroy other bacteria which are the cause of mixed infection. They cannot furnish recuperative power when the system is totally undermined. In short, they cannot overcome the consumption which has taken place as a result of the tuberculous process. Yet this is what many have expected a specific remedy for tuberculosis to do.
>
> Specific products made from the tubercle bacillus are remedies which, when combined with other suitable therapeutic measures, offer the best possible chance of cure to those suffering from tuberculosis in any stage; but

[1] Pulmonary Tuberculosis, William Wood & Company, 1908.

from their uniformly good results in early tuberculosis they demand an early diagnosis and their early intelligent employment. In advanced tuberculosis no more should be expected than is possible to be obtained.

Enthusiastic from the brilliant results obtained in the treatment of diphtheria by antitoxin, many have made this their standard of a specific remedy. If the therapy of all infectious diseases was as simple in principle as that of the application of antitoxin in the treatment of diphtheria, they would soon be conquered by medical science. It must be remembered, however, that antitoxin does not always cure. If administered late, the life may be lost. A remedy may be specific and yet not be able to cure all the different pathological conditions that are present in a disease. Tuberculin is a specific in tuberculosis—that is, its action is such that it calls out a physiological response on the part of the immunizing mechanism of the body, and in that way aids in specifically overcoming tuberculosis. The particular indication for its application as a remedy is in early tuberculosis. While not contraindicated in advanced tuberculosis, yet it must not be expected to have the same action when hampered by necrosis, fibrosis, and impaired functions on the part of the various organs, as it does in early tuberculosis. It should not be expected to overcome necrosis and the changed conditions which we find in advanced tuberculosis; yet a great deal of the adverse criticism directed against this remedy is based on its inability to do these impossible things.

Tuberculous Infection.—In order to understand tuberculin and its action it will be necessary for us to discuss the tuberculous infection and the way in which the system overcomes it, or is overcome by it, and also to call attention to some important points in the pathology of the disease. Our conception of infection in tuberculosis is that the fight between the organism and the disease-producing germs begins soon after birth. Statistics show that tuberculosis is not inherited, except in a sufficient number of cases to prove it to be a pathological possibility; neither does infection occur commonly during the first few months of life, but as time goes on, we find the number of infections increasing. The numbers keep increasing as the child grows older, so that by the time the fifteenth year is reached a very large proportion of children are infected.

H. Albrecht, discussing the subject, presented a paper before the fifteenth meeting of the Association of German Pathologists, which met at Strassburg in April, 1912. This paper contained the following interesting statistics:

Of 100 post mortems made upon children in the ages of six to sixteen years, in one of the hospitals in Vienna, he found active clinical tuberculosis 38 times. Of 62 cases which did not show active clinical tuberculosis, 36 presented macroscopical tuberculosis, and 13 more showed infection of the glands upon microscopical examination; thus 87 per cent of these children were pathologically tuberculous. Of those between the ages of six and sixteen years, 92.3 per cent were tuberculous. Of those which did not show any clinical signs of tuberculosis, 79 per cent had pathological tuberculous lesions.

This is quite remarkable in that it confirms the findings of the tuberculin tests which have been given by Hamburger, von Pirquet, and others; and as we recall the painstaking work of Bartel, which shows that the lymph-glands may harbor tubercle bacilli in sufficient numbers to produce infection and yet show no signs microscopically, we are probably justified in suspecting that quite a proportion of the rest of these children might be infected.

The question of the source of infection is a very difficult one. Just how the tubercle bacilli are carried into the human body in particular instances we do not know. The only thing we do know is that bacilli are so common that in nearly all instances the child has taken sufficient numbers into his body to infect him before he is fifteen years of age. The danger of infection depends upon the intimacy and duration of contact with bacilli; therefore we find the greatest percentage of infection in families where the children are associating with those who have the disease. Cohn, cited by Römer,[2] gave the cutaneous tuberculin test to 273 children of tuberculous parents and found as follows:

Of those from	2–3	years,	66	per cent	gave	a	positive	reaction
	4–5	"	60	"	"	"	"	"
	6–7	"	77½	"	"	"	"	"
	8–9	"	77	"	"	"	"	"
	10–11	"	80½	"	"	"	"	"
	12–13	"	89.9	"	"	"	"	"
	14	"	100	"	"	"	"	"

[2] *Brauer's Beiträge zur Tuberkulose*, Bd. XXII, 1912.

The following tables from Hamburger[3] show the percentage of children reacting in the St. Ann Kinderspital, Vienna.

Hamburger examined 509 children who entered St. Ann Childrens' Hospital in Vienna, suffering from diseases other than tuberculosis. Of these, 233 were suffering from scarlet fever, 253 from diphtheria, 13 cerebrospinal meningitis, 6 typhoid, 1 osteomyelitis, 1 perityphlitis, 1 inguinal hernia, and 1 fracture of the femur.

These children were tested first by the cutaneous method of von Pirquet. Those who were negative were given from 0.1 to 1 milligram of tuberculin subcutaneously, two days later. To those who were still negative another injection of 1 milligram was given. Those which showed no reaction following these various tests were considered free from tuberculosis. Of these 509 children, 271, or 53 per cent, reacted to tuberculin. Hamburger does not state at what period he gave these tests, and we do not know whether he took into consideration that these various infectious diseases have some effect in reducing the reactive power of the patient, as mentioned elsewhere in this monograph. If he did not take that into consideration, we must believe that more than 53 per cent of the 509 children would have reacted had the test been made at a time when they were not suffering from infectious diseases. If we consider these children according to their age period, we find as follows:

NUMBER OF CHILDREN	AGE PERIOD	NUMBER REACTING	PER CENT REACTING
46	2	4	9
56	3	11	20
75	4	24	32
50	5	26	52
63	6	32	51
46	7	28	61
30	8	22	73
35	9	25	71
26	10	22	85
29	11	27	93
19	12	18	95
17	13	16	94
17	14	16	94

The author, in discussing this table, says that he makes no claim to absolute exactness, for the number of patients in each individual year is too small; therefore we can only say that it is relatively correct. He then considers that it is better to show

[3] Pathologie und Diagnostik der Kindertuberkulose, Wein, 1910.

these in age periods, wherein the gradual increase of infection as the child grows older is shown to better advantage. This he shows in the following table:

AGE PERIOD	NUMBER OF CHILDREN	NUMBER REACTING	PER CENT REACTING
1 year	23	doubtful	1
2 "	46	4	9
3–4 years	131	35	27
5–6 "	113	58	51
7–10 "	137	97	71
11–14 "	82	77	94

Most surprising of all are the statistics of Jacob, cited by Römer,[4] who gave the cutaneous tuberculin test to 2744 children in the country districts of Hanover. Of these, 1927 were between the ages of six and fourteen years, and 817 between the ages of six months and six years. There reacted of those who were of a school age 45.9 per cent. Even of those in the first school year, 35.6 per cent reacted; while of those in the last school year, 64.4 per cent reacted.

Jacob further examined children in villages in which no clinical tuberculosis had existed for years and found that from 30 to 40 per cent of them reacted to tuberculin. These statistics are intensely interesting, because they show that if we are going to prevent tuberculosis we must begin in childhood. Most alarming of all, these statistics teach that tubercle bacilli are so generally scattered that they are a great source of danger even far from the host which cast them off. They show us further that children, even at an early age, are subjects for tuberculin therapy. They further show us that children develop sufficient immunity to overcome infection or at least hold it in check in a large per cent of cases.

From the statistics just given we see that tuberculous infection is very common, and believe that it is conservative to say that at least 75 per cent of all children are infected with tuberculosis before their fifteenth year. Bacilli are so common that they reach the child in one way or another in sufficient numbers to produce infection in nearly all instances before the age of childhood is passed.

Infection and Immunity.—Coincident with infection there develops in early childhood a resistance to the disease. Our

[4] *Brauer's Beiträge zur Tuberkulose*, Bd. XXII, 1912.

modern studies have given us a very different idea of the term immunity from that held by us a few years ago. Immunity does not mean what we formerly thought it, an impossibility for an organism to become infected with a disease, but a resistance to the disease. Immunity is a relative matter. It differs with individuals, also with infections. When bacilli enter the body certain phenomena occur. We must assume that the child has some natural protection against bacteria; so, when the first bacilli enter the body, if the number is not too great, they are destroyed. As they are destroyed their bodies go into solution, and the specific products (proteins) contained in them are set free. These stimulate the cells of the body, and as a result certain protective substances are formed. It seems to be a law of nature that a given portion of toxin will excite the cells to the production of many times the amount of antitoxin necessary to counteract the toxin which causes the stimulation. Therefore, after the first inoculation with bacilli, the child's body is more resistant to tuberculous infection than it was before the bacilli gained entrance—that is, it contains more protective antibodies. It is not long, however, before a greater number of bacilli are taken in. These too may be destroyed, and still more antibodies result. Sooner or later, however, sufficient tubercle bacilli enter the child's body to overcome the protective forces. The result is infection. The bacilli settle themselves in the tissue. They are surrounded at once by leucocytes. A proliferation of cells occurs, and soon the tubercle bacilli have a wall thrown about them. Inside of this protective wall they multiply. It may be that the defensive properties of the tissues may soon be able to overcome this infection, and healing may result. If the number of infecting microorganisms is larger, however, they will probably multiply, and the disease will spread from this point to adjacent tissues or to distant parts of the body, thus producing new foci of infection. It is possible for the infection to spread, even though considerable immunity is present.

In these early infections when the tubercles are small and before serious changes have occurred in them, the factors which favor spontaneous healing, as well as the measures employed artificially, act to best advantage. The reason for this is very evident, for the next change which occurs in the tubercle is

very unfortunate in that it greatly increases the difficulties of cure. The tubercle undergoes necrosis. The amount of necrosis differs considerably in different infections. In latent infections, or in those of a fibroid form, there is very little; while in active infections, especially of the ulcerative type, the necrosis is very widely spread. The amount depends on the activity of the bacilli, being greater when they are multiplying rapidly and producing large quantities of toxins. There are other things which make us believe that necrosis is, at least in part, the result of enzyme action. Diminished vascularity of the tubercle has also been assigned as a cause, but I feel that we have equally good reasons for considering this a result of necrosis rather than a cause. The results of necrosis differ greatly. Sometimes the tubercles are small and scattered; at other times there are numbers fused together, and the mass becomes exceedingly large. The common result of necrosis is destruction of tissue and cavity formation. Of course, in these very small tubercles the cavity is negligible, but where numbers of the tubercles are fused together, and necrosis occurs, very large cavities are often formed. Sometimes these are almost coextensive with the lung itself. These conditions occur in spite of the body fluids containing protective substances in greater or lesser amounts. These areas of necrosis are usually surrounded by a wall of cells. The blood supply is shut off from them; consequently, no matter how many antibodies are present in the blood itself, they enter the tubercle with difficulty or not at all, and thus are prevented from destroying the bacilli contained therein. Therefore, it is possible that a patient may die of tuberculosis and still have a high grade of immunity present; nevertheless, as I shall discuss later, a high grade of immunity in all these cases is very desirable, because it will help to prevent the spreading of the disease to other parts and thus add its part in saving the patient from destruction.

Evidences of Immunity in Tuberculosis.—Formerly it was generally understood that there was no such thing as immunity in tuberculosis. It was noticed that, unlike many of the infectious diseases, a patient who had tuberculosis, though he should recover from it, was more prone to break down with it again than one who had not previously had the disease. It was explained on the ground that, instead of an immunity resulting from the

first attack, an increased susceptibility developed. It is now known that while the observation is probably correct the explanation is faulty. If a man who has had tuberculosis obtains a healing, and then develops the disease again, he develops it in spite of an immunity; the reason being that the bacilli are not all destroyed and remain in the tissues where, for one cause or another, they become active again and produce clinical symptoms; or it might be that a new inoculation with sufficient numbers of bacilli has taken place from without to overcome the immunity which has developed as a result of the former active lesion.

In early tuberculosis we know that there is a degree of immunity present. This immunity increases as the disease goes on and lasts as long as life exists. The extent of this immunity can be seen from the following observations. Römer, Vallée, and others have shown that an animal which has a tuberculous lesion, though slight, or one from which it has healed, has a marked immunity to further inoculations of virulent bacilli. That advanced tuberculosis is accompanied by a marked immunity is shown by the fact that patients who have advanced tuberculosis are compelled to withstand inoculations of large numbers of bacilli at frequent intervals. For example, every patient who has advanced tuberculosis has myriads of bacilli passing through his intestinal tract, from swallowing sputum, daily without infection occurring. He has sufficient quantities of them in his air-passages to produce inoculation in healthy persons constantly. And as has been shown by Rosenberger, and confirmed by many others, those in the advanced stages of tuberculosis suffer more or less from a bacillemia. Every now and then bacilli break into the blood-stream; yet this may happen for months or probably years without infection occurring. Thus it can be seen that the disease, tuberculosis, confers a marked immunity upon the individual affected.

This immunity is also subject to demonstration by various laboratory methods and by our tuberculin tests. In those suffering from a slight tuberculous infection, hypersensitiveness of the tissues to tubercle bacilli as shown by the oft-quoted experience of Koch on reinoculation and to tuberculin is very marked, and the cells of the body are able to respond rapidly in the formation of immune bodies and in the production of the tuberculin reaction. In advanced tuberculosis insensibilty to tuberculin is

present, and response on the part of the body cells is more difficult to obtain. There may be two factors in this insensitiveness: first, the fact that the body has been subject to discharges of tubercle toxins for so long and in such large amounts that it is able to withstand large doses of tuberculin without calling forth a general reaction; or, secondly, it may be due to a lack of ability on the part of the tissues to form antibodies necessary to produce reaction.

Such observations as those of Römer, Vallée, Calmette, von Pirquet, and Wolff-Eisner place a new and practical interpretation upon the original observations of Koch, that an animal which is previously infected with tuberculosis reacts differently to a second inoculation than an animal which is free from the disease. The experiments of these men have shown that the first infection gives a marked immunity to the second infection; and in this way, they explain the fact that a secondary inoculation in one who is previously infected, unless the inoculation be of an enormous number of bacilli, is apt to take a chronic course and produce an infection of low virulence. I have often made the clinical observation that a patient who had quite a marked infection years previously and then developed the disease again suffered from an infection of lighter virulence than one who was not so protected. The cases of tuberculosis which are most rapid are those which come in patients from races or families who have not had tuberculosis and who have probably received their infection in the prime of life, or at least have received their extension at that time. While the patient takes a great deal of comfort in saying, "There has never been any tuberculosis in my family. I have always been strong and never had anything like this before," the trained clinician knows that this in itself is a disadvantage rather than an advantage. A great advantage lies with the race, the family, and the patient that have struggled against the disease previously, because a certain amount of immunity has developed which can be turned to the patient's account in rendering the tubercle bacilli less active, hence producing a less virulent form of infection. In case of the patient the statement should be modified to mean a slight infection, for, if the disease has been extensive, other factors come in which overbalance any advantage that might result from an increase of the specific immunizing bodies of the blood. In

these observations we have an indisputable argument in favor of tuberculin. The substances which produce this immunity are the tubercle proteins (tuberculin).

Artificial Immunity in Animals.—The artificial immunization of animals against tubercle bacilli forms one of the most interesting as well as most fruitful studies connected with the subject of tuberculosis. The studies along this line have given us eventually a fairly clear idea of the infection as it occurs in man. While it has been impossible to use many of the methods on man that have been employed in animals, yet the study of the process in animals has clarified our theories and given us useful hints for study in man.

Some German and French experimenters were able to produce a certain degree of immunity against virulent cultures in the late eighties and early nineties. Trudeau [5] reported his experiments by which he produced an appreciable immunity in rabbits by the use of living avian bacilli in 1892. These were followed by de Schweinitz, Pierson and Gilliland, and von Ruck in America. Numerous investigators in Europe have immunized animals, among whom are Denys, Calmette, Spengler, and von Behring. Aside from these, many other important successful experiments were made, which soon established the fact beyond any doubt that an infection by living non-virulent bacilli gives a positive immunity against further infection. So far, no safe method has been established whereby this may be carried out generally on human beings.

It remained, however, for Römer [6] to show the great import of this fact in its bearing upon clinical tuberculosis. With untiring energy he has performed experiment after experiment which shows that we, as a race, are constantly taking advantage of the fact that a slight infection offers protection against further inoculations. From this we are led to assume that the infections in early childhood are producing an immunity and building up a protection within the host, which is probably saving the race from destruction from tuberculosis.

Artificial Immunity in Human Beings.—From this we cannot argue that infection in early childhood is desirable, but rather that, if it occurs, we should see that it heals so that we may turn

[5] *New York Medical Journal*, July 23, 1893.
[6] *Brauer's Beiträge zur Tuberkulose*, Bd. II, v. 79, 1908.

it to the patient's advantage; for, by so doing, we cure the disease and leave the patient with an immunity against further infection. These experiments on immunization of animals show that artificial immunization is practicable. A careful analysis of the knowledge derived from them also points to the fact that tuberculosis can only be controlled by some immunizing vaccine.

Baldwin,[7] discussing this interesting question, says:

> One fact has been prominent in the course of all investigations, and that is the superiority of living bacilli over all the preparations of dead bacilli for protective inoculation. The vital element has a more pronounced influence, even upon animals which completely resist infection by the immunizing vaccine and show no trace of the inoculated bacilli a short time afterward in their tissues. It is natural to suppose that the bacilli perish too soon to adjust themselves to a parasitic existence by producing any hypothetical secretion which might be the secret of their greater protective influence. It is admitted, however, that the degree of immunity is directly proportional to the virulence of the vaccine. The subtle difference between the immunizing value of living and dead bacilli needs more investigation, likewise also the cause of variations in virulence.

In this connection the experiments of Klemperer and C. Spengler in injecting themselves with virulent bovine bacilli are interesting. The work of Webb and Williams in producing immunity by gradually increasing the number of living bacilli used in the inoculation is worthy of note, as are also Friedmann's experiments.

Maragliano made an immunizing product from the tubercle bacilli for which he claimed some efficiency several years ago, but it has not been used extensively. His idea was to produce a small localized ulcer which would heal and leave the individual protected.

The latest effort which deserves our attention is that of von Ruck,[8] who reports on 339 children whom he has treated by a vaccine prepared from tubercle bacilli. This vaccine is made up as follows:

Protein No. 1	0.25	mgs.
" " 2	2.75	"
" " 3	1.00	"
" " 4	6.00	"
Fatty extractives	0.01	"

[7] Sixth International Congress on Tuberculosis, vol. I, part I, page 174.
[8] *Journal of the American Medical Association*, May 18, 1912.

The preparation of these proteins is given by the author[9] as follows:

The culture of tubercle bacilli used is of human origin, grown on bouillon, and has been perpetuated in my laboratory for the last ten years; it was apparently avirulent when first tested upon guinea pigs and has continued so to the present time. In the manufacture of the preparation heat has been avoided, and the chemical effect of light excluded. No chemicals have been introduced in kind or concentrations that could injure, split, reduce, or alter the several constituents.

The cultures, having reached their maximum growth, are collected upon a filter and washed free of adhering culture fluid until the filtrate gives no further biuret reaction.

The bacillary mass is then transferred to a glass container immersed in distilled water containing 0.4 per cent phenol, and with frequent stirring and shaking it is macerated for several days, when the filtrate obtained contains the protein designated as No. 1. Chemically examined it shows primary proteose 25 per cent, secondary proteose 70 per cent, peptone small amount. Reaction acid.

After further washing with distilled water the bacilli are dried and powdered, when their fat extraction follows; after drying they are again powdered and then partially extracted in distilled water, yielding Protein No. 2, this showing coagulable protein 0.03 per cent (estimated by nitrogen), primary proteose 48 per cent, secondary proteose 50 per cent, peptone trace. Phosphorus content 0.1 per cent; reaction alkaline.

The bacillary mass is again dried and powdered and suspended in 0.4 per cent carbolized distilled water and then ground wet in glass capsules with agate marbles, until repeated microscopic examinations no longer show a fragment or formed substance of the bacilli. Filtration through porcelain gives Protein No. 3 in solution, differing from No. 2 by absence of coagulable protein, the relatively small amount of primary and increased amount of secondary proteose (75 per cent). Peptone is shown in small amount. The phosphorus content is 0.5 per cent; the reaction acid.

Protein No. 4 passes the filter after the addition of a 0.4 per cent solution of sodic hydrate and gives all reactions for nucleoprotein. The remaining bacillary residue, amounting to about 5 per cent weight of fat-free tubercle bacilli free from proteins (nitrogen determination), may contain traces of fats and is probably cellulose.

The secondary proteoses give no reaction for sugar.

The fatty extractives of tubercle bacilli may be obtained separately as neutral fats and fatty acids by their saponification and subsequent extraction of the acid precipitate with alcohol and with ether, or, in order to avoid undesirable chemical changes by saponification, the alcohol fats and ether fats may be obtained respectively by first complete extraction with ether, followed with alcohol, and vice versa, which to me appears preferable. When in solution they can be shaken out with distilled water, the latter holding

[9] Report from the von Ruck Research Laboratory for Tuberculosis, No. 1, June 1, 1912.

about 0.5 per cent in free suspension, which is opalescent in appearance in that concentration; the opalescence disappears in the concentration employed by me.

The several proteins and fatty extractives having been obtained separately and having each been standardized, any free alkali in Protein No. 4 having been neutralized by addition of a weak solution of HCl, just short of causing precipitation, the several constituents are assembled to represent the formula given in the text.

The precautions employed in preventing injury or undesirable modifications of the several bacillary products have not all been demonstrated as absolutely requisite for their highest efficiency, my purpose in their adoption having been to take no chances of an inferior preparation by their omission.

The author further states:

Having shown the prompt and uniform development of all specific antibodies after a single dose of the preparation by the method described and the induced immunity being still evident in like degree in every case re-examined three to eight months later, and after a lapse of eight years in the one case in which I made the first trial, and having further confirmation in regard to the endurance of the induced immunity by the fact that I have in numerous instances been able to show the same permanency in therapeutic immunization with one of the constituent proteins after periods of two to fourteen years, I proceed now to the relation of experimental studies designed to show that the method is ample to protect against virulent infection.

Not only has von Ruck been able to immunize children, as he is able to show by their blood containing all of the specific antibodies to tuberculosis after a single dose, but the blood of the patient is able to produce lysis of tubercle bacilli *in vitro*, and when mixed with virulent bacilli prevent them from producing the disease in guinea pigs.

While this work still remains to be confirmed, let us hope that it will stand the test of scientific investigations and afford us this great boon for which scientific men have been seeking. If it is not perfect, it may at least be a forward step in the final solution of the problem.

Latency.—The term "latency" is used in tuberculosis to describe an infection which, though not entirely healed, is yet kept in abeyance for a period of time. The battle may go on between the infection and the protective forces of the body for years without either gaining any particular headway. The immunizing powers of the body may not be able to destroy the bacilli and heal the infection, neither may the bacilli be able to multiply and increase the area of the infection. It is essential to under-

stand this condition of latency if we desire to fully comprehend clinical tuberculosis. The splendid work of Römer, von Pirquet, Hamburger, Wolff-Eisner, and others has shown us definitely the importance of fully understanding the latent stage of tuberculosis. The experimental work of these observers, particularly that of Römer, shows that infection may not be healed and yet a patient may have considerable immunity, probably sufficient to protect him from all ordinary inoculations of moderate numbers of virulent bacilli coming either from without or from the focus of infection within. In fact, there is evidence which goes to show that it is probable that many, some even believe most, of the infections in later life are not due to inoculations from without, coming on immediately prior to the time that clinical symptoms manifest themselves, but rather that the disease is due to a spreading from an old focus within the body, something occurring which causes the protective walls of the tubercles to break down, thus allowing the bacilli to escape in sufficient numbers to produce an extension or a new infection in some other part.

The importance of this is readily perceived. It shows the danger of latent tuberculosis. It must be remembered that latent tuberculosis is not healed tuberculosis. Any tuberculosis which produces symptoms every now and then, even though they be slight, cannot be looked upon lightly and should be considered as a danger. It is characteristic of latent tuberculosis that it every now and then throws out specific toxins into the tissues which stimulate the cells to the production of an increased number of antibodies. The result is that these infections, in this manner, keep up a more or less constant irritation of the mechanism of immunity and therefore keep the patient more or less resistant to the disease. While the infection does not heal, yet this increased defensive force keeps the disease from spreading.

When these toxins pass from the latent focus, if the quantity is only slight, there may be no recognizable and no untoward symptoms following it. On the other hand, if the quantity is large, clinical symptoms are produced. The patient usually feels somewhat tired and nervous, and if it persists for a long time, the patient has a feeling of depression and of being run down. Sometimes, if there is a very large quantity thrown out suddenly, it is followed by the same symptoms that are produced

by a tuberculin reaction. When these symptoms occur often or become pronounced, we must consider that the latent focus is becoming active and that there is danger of the process assuming a state of acute inflammation with a spreading of the infection.

The latent focus, therefore, is not a danger so long as it remains latent. On the other hand, it must not be looked upon lightly, for it is a condition that may become a danger at any time. Every now and then from this latent focus sufficient bacilli are thrown out to produce a new infection, this, in spite of the fact that a fairly high degree of immunity may be present. If we, as clinicians, could know just when these latent foci are going to become active, and if the patient could be put upon treatment at that time, the mortality from tuberculosis would be very slight, but the determining of this condition is attended by so many difficulties that it is not practicable. Therefore, I think, as clinicians, we are going to be forced to pay more attention to latent tuberculosis than we have in the past, and consider it as seriously as we do latent syphilis and quiescent appendicitis or cholelithiasis; at least we will consider every case as one of clinical tuberculosis until all signs and symptoms, no matter how slight, have permanently disappeared.

Curability of Latent and Early Active Tuberculosis.—It can be readily gathered from our discussion of the action of tuberculin that it is specific in that it acts upon tuberculous individuals differently from what it does upon healthy; and in that its action in a tuberculous individual calls forth a specific immunizing response in the formation of lysins and antitoxins; and that it further elicits a specific reaction in the focus of infection together with the attending phenomena which are favorable to cure. Nevertheless, in spite of this, cure does not always result either spontaneously or when tuberculin is administered. The blood may be surcharged with specific lysins and antitoxins and yet be unable to reach the focus of infection, because of the fact that the blood-stream is shut off from the center of the tubercles. Especially is this true as the tubercles take upon themselves advanced pathological change; therefore the ideal conditions for tuberculin treatment are found in early tuberculosis, while the tubercles are still small and it is possible to apply the body fluids intimately to them. If this limitation of tuberculin

be understood, it should spur us on to its application at a time when this disadvantage is as small as possible. We know that diphtheria antitoxin will not cure diphtheria after the cells have been destroyed by toxins; so do we know that tetanus is incurable after the toxin has become fixed in the central nervous system. We do not consider these limitations as arguments against these two antitoxins, but we consider them as indicating to us that we must apply them before these serious conditions occur; so should we draw the same conclusion with reference to tuberculin. Employ it at a time when it is indicated, when the antibodies resulting from its application can be applied to the focus of infection and when the resulting inflammatory focal stimulation can have comparatively healthy cells to act upon, and not wait until necrosis and advanced pathological changes have occurred which are unable to be affected by it.

In our urging the treatment of tuberculosis when the infection is small we are supported by pathological evidence. Pathologists have shown for a long time that early tuberculous infections heal spontaneously in a very large per cent of cases. The reports of Naegli and Burckhardt are especially convincing on this point. Pathological evidence, on the other hand, shows us that, while advanced tuberculosis has a tendency to heal, healing occurs only with the greatest difficulty. Therefore, if tuberculosis is to be healed and if the specific action of tuberculin is to be applied at the time when it has the most advantages, it behooves the clinicians to treat the infection while the lesion is small and while the pathological process is comparatively simple. I am fully cognizant of the fact that tuberculin is of great value in the treatment of advanced tuberculous processes and would not be misunderstood to the contrary; but I cannot help feeling that we are wasting myriads of precious lives in employing it late instead of early at the time when healing is the exception instead of the rule.

Action of Tuberculin.—The action of tuberculin has been a subject of much discussion and speculation. Many different theories have been offered as to its method of action. Because of this fact the remedy has been more or less discredited. One would think, however, that any physician who has dealt with as many remedies as we are compelled to deal with, without knowing exactly how they produce the action that they do, would be

lenient toward tuberculin and not hold up against it the fact that we do not wholly understand its action.

Clinically, we do know its action, the same as we know the action of the pharmacopeial remedies; that is, we see certain results which follow its application in a sufficiently large proportion of instances to insure that they are the definite results of the remedy; but when it comes to a full explanation as to just how this result is brought about, we are left somewhat to speculate, the same as we are with digitalis, ergot, belladonna, and other commonly used remedies. Who can explain fully the action of an ordinary bath? I think, however, that a theory of action can be given which is sufficiently satisfactory to guide us in therapy and to show the definite good or harm that may be produced by the administration of this remedy.

The cure of early tuberculosis—that is, the cure of tuberculosis even before necrosis occurs—is not a simple matter, and the cure of tuberculosis in its advanced stage is a very complex proposition. The action of tuberculin is best suited to early tuberculosis, although it is of value in tuberculosis of any degree of advancement.

The name tuberculin embraces all the products made from tubercle bacilli which contain their bacterial proteins. It is a specific remedy in that its injection into the body will produce a specific reaction in individuals suffering from tuberculosis and in that it is able to call forth a specific immunizing response on the part of the cells of the invaded organism and stimulate the diseased foci to healing.

There has been much effort expended on the part of various investigators to produce new and improved preparations, and it must be said that some preparations seem to be better than others; but as Wolff-Eisner has shown, and as is now generally accepted, all tuberculins depend for their action upon the same principle—that is, the specific bacillary protein; and the difference in the various products is largely quantitative rather than qualitative. When we discuss tuberculins then, it is not necessary to speak of them individually and enter into a detailed description of each one and give the particular claims for each, but to speak of them in a general way, because the action of one is practically the action of all. There is probably some difference in the action of dead tubercle bacilli, or the bacillary

protein from the dead tubercle bacilli, and protein from living tubercle bacilli; at the same time, their action is analogous, and the result of their action is much the same. It is probable also that there is some difference in the protein from bacilli grown on different media and in those grown on artificial media in general compared with that produced from the lysinized bacilli which have grown in the body. It is also probable that there are several different kinds of protein in bacilli and that the products may differ as they differ in the quantities of these individual proteins.

Dead tubercle bacilli or tuberculins will produce histological tubercles the same as living bacilli. This indicates that the specific stimulation that produces the peculiar arrangement of cells, which is characteristic of the tubercle, is likewise contained in the proteins separated from the bacillus.

The healing of tuberculosis is a complicated matter. It is not simple like the antitoxin cure of diphtheria; so those who are giving an opinion as to whether tuberculin is specific must bear in mind that it might be specific and still not be so direct in its action as antitoxin is in diphtheria.

The original focus of infection in tuberculosis never kills anyone, but it is the extension from this focus that produces death; so in order to combat tuberculosis two things are necessary: one is to prevent the disease from spreading; the other is to stimulate a healing of the focus that exists. It can be shown that tuberculin answers both of these purposes.

Tuberculin is usually spoken of as a toxin. In its general application this is incorrect. Tuberculin is not a poison. It can be injected into healthy human beings or healthy animals in large quantities without doing harm, as previously mentioned. Its action on the tuberculous, however, is very different. Tuberculous animals and tuberculous human beings are sensitive to it, and in them it produces a specific action which is very different from that in the healthy. The healthy individual will usually bear 10 milligrams of Koch's old tuberculin without producing any reaction. Some will tolerate several times this dose. New-born babes have been given very large doses, such as would call forth a violent response on the part of tuberculous adults, without the least disturbance of their well-being. Koch gave to himself 250 milligrams at a single dose, and while he devel-

oped severe symptoms accompanied by chill, high fever, and severe prostration, yet it passed off without harm. Healthy guinea pigs will tolerate one or two grams of Koch's old tuberculin without suffering any harm; while these same amounts or even smaller quantities will produce marked reaction in individuals or animals suffering from tuberculosis. This emphasizes the fact that tuberculous individuals are sensitive to the tubercle protein contained in tuberculin.

The best theory of tuberculin action is the one proposed by Wolff-Eisner. Personally, I accept it as a working basis, although I have amplified it and tried to fill in gaps which make it fit the conditions more fully. I offer this as one which seems to furnish a clear and fairly consistent explanation of the action of tuberculin as a test for the presence of tuberculosis and as a therapeutic measure. (I shall repeat in part what was stated on pages 4 and 37.) Wolff-Eisner assumes that either tuberculin, or the tubercle bacillus when it enters the body stimulates the body cells and calls forth the production of specific antibodies known as lysins. These circulate in the blood ready to destroy any tubercle bacilli, or tubercle protein, that are introduced into the body. As a result of the action of these lysins the tubercle bacilli, or tuberculin, are split up into highly toxic substances, which in turn stimulate the cells further and probably produce certain irritative actions within the focus of infection. As a further action it is supposed that the tuberculin stimulates to further lysin production and that the toxins which are set free by the lysins stimulate to further antitoxin production. Therefore, we assume that there are two groups of antibodies in the production of immunity in tuberculosis: first, the lysins, and second, the antitoxins. The lysin is necessary for the first destruction of tubercle bacilli. It stands ready to defend the organism at any time when tubercle bacilli, or tubercle protein, are introduced into the system. The antitoxin, on the other hand, stands ready to destroy and prevent harm resulting from the amount of toxin which is set free as a result of the lysis. If it were not for the former, the bacilli would not be destroyed; and if it were not for the latter when they were destroyed, especially in large numbers, the organism would be overcome by the toxins which would be set free. From this I think we can very well understand the action of tuberculin in its production of immunity to tu-

bercle bacilli. In the healing of a tuberculous focus, however, there is still another factor: the stimulation of the focus of infection.

When tuberculin is injected into the body of one infected with tuberculosis the first phenomenon that occurs results from its meeting the specific lysins. After a period of a few hours, which corresponds to the period of incubation in infection, the tuberculin is destroyed by the lysins, and the toxins are set free. This period varies in length of time, and its end is marked by the onset of the phenomena of reaction. If the toxins which are set free are small in amount, and the body fluids are surcharged with their specific antitoxins, the reaction response on the part of the organism is unattended by any recognizable phenomena. It is probable that the general reaction, as well as the focal reaction, depends on these secondary toxins produced as a result of the action of the lysins upon the tuberculin.

It is necessary to bear in mind that the specific antibodies are found under two conditions: anchored to the cells, and circulating free in the blood. The toxins circulating in the blood come in contact with the free-circulating antitoxins and are for the most part rendered innocuous. There are some, however, whose combining power remains unsatisfied until they reach the focus of infection, where they meet antibodies anchored to the cells with which they combine and produce a stimulation of the tuberculous tissue, resulting in what we term a focal reaction. The strength of this focal reaction depends upon the energy of the action between the toxins and antitoxins in the focus. If the dose of tuberculin is small, no appreciable focal reaction occurs. If it is slightly larger, we assume that a slight irritation resulting in hyperemia, as seen in visible foci, occurs. If it is still larger, a severe congestion takes place, which in extreme cases results in the destruction of tissue.

The general reaction, according to this theory, is caused by the free toxins circulating in the blood after all free antitoxin has been used up. If the amount is very small, no effect is appreciable. If it is a little larger, the usual symptoms of slight toxemia appear: a slight nervousness, an irritability, and feelings of malaise, which soon pass away. If the amount is greater, a distinct aching is felt, which may be accompanied by a chill and rise of temperature. That this is not due to the tuberculin

per se but to the toxins is indicated by two facts: in the first place, a general reaction, likewise a focal reaction, does not occur until after a period of incubation, not until the tuberculin has been in the tissues for some time; and in the second place, the symptoms are identical with those produced by the absorption of any other toxins in the body.

What happens in the tuberculous focus during tuberculin treatment is a question which we must now attempt to explain according to our theory. We know from animal experimentation that a tuberculous focus heals through inflammation. If, as shown by C. Spengler, an experimental tuberculous infection is produced in the ear of a rabbit and only sufficient tubercle bacilli used to produce a slight infection, this will settle down and become localized. A nodule forms which remains stationary. If, then, a second inoculation of tubercle bacilli is given, the first nodule becomes inflamed, and as a result of the inflammation, progresses toward or goes on to a healing. This is also in harmony with what we have noticed clinically in tuberculosis. If the process is a visible one, we see this same inflammatory process accompanying favorable clinical change. In the tuberculous focus there are substances probably always present which produce reactions, and as a result of these reactions, healing is promoted; so, after the tuberculin has been acted upon by the lysins and converted into more toxic bodies, these latter have a secondary healing effect when they reach the foci of infection, by producing reaction. This reaction has long been recognized in tuberculin therapy as a focal reaction. It may be produced artificially by injecting living bacilli or the bacillary protein (tuberculin) of dead bacilli into the body. To the eye it consists of a hyperemia; or, if of greater severity, a congestion. As a result of the focal reaction more blood is brought to the part, and the antibodies, lysins, and antitoxins circulate more freely about the focus of infection where the healing must take place. Any extra amount of endotoxins that are thrown out from the tuberculous process are acted upon by the specific antibodies and rendered innocuous, and any bacilli with which the lysins come in contact are destroyed, unless they are in such large numbers that the lysins present are unable to satisfy them. It would seem from this explanation that focal stimulation is probably much more readily produced in spontaneous cure than in artificial tu-

berculin treatment, because the toxins resulting from the destruction of the tubercle protein meet their antitoxins as soon as they are liberated, without escaping from their focus of infection. This suggests also that the increase of dosage is necessary to produce perfect focal stimulation.

Aside from this action, which consists of a more intimate application of the antibodies which have been formed by the tuberculin, there is also a gathering of the lymph and leucocytes, which probably has some effect in destroying the toxins and reducing the vitality of the bacilli. Enzymes are also probably set free, and their action is hastened. There is an increased stimulation to the production of fibrous tissue, thus aiding in scar formation and encapsulation. It is further probable that the original explanation by Koch that this inflammatory reaction helps to separate the diseased tissue from the healthy is partly true.

Why Use Tuberculin Where Spontaneous Cure Fails?—It might be asked why the spontaneous cure of tuberculosis so often fails and what advantage can be had from the artificial administration of tuberculin under such circumstances. Our answer to these questions must be more or less theoretical. That tuberculosis fails to heal spontaneously in some instances is probably due to the fact that the original infection is too severe for the antibodies, which are present in the organism, to overcome. Either there are too many bacilli or the virulence of the bacilli is too great, or the specific immunizing substances found in the organism are deficient at the time infection occurs, thus enabling the infection to obtain a strong foothold. In this connection the question of individual resisting power, a temporary or permanent failure on the part of the organism to furnish the proper response in immunizing bodies when the specific stimuli are furnished by the invading bacilli, must be considered. Under these circumstances, after the infection occurs, the local pathological changes probably take place quite rapidly, thus enabling the infection to become well established before the immunizing substances in the organism increase in such numbers as to be able to cope with it. Thus, an infection occurs and rapidly gains advantage over the organism, which makes healing difficult. All this time, however, the specific toxins are being thrown out from the focus of infection, which stimulate the physiological machinery of immunization and call forth the production of antibodies,

but even if the response in antibody formation should be greater after a little time, we can still conceive of its being too late for a healing to result.

In explanation of why the response on the part of the organism to this natural discharge of toxins from the focus of infection is not sufficient to produce so great a healing response as is produced by the artificial injection of tuberclin, we assume: First, that when the toxins are thrown out from the focus of infection they meet the cells adjacent to the lesion which are more or less injured by the pathological process; consequently there results from this a less favorable response than would occur if the stimulation took place in healthy cells. Second, that these toxins escaping from the focus of infection are given off irregularly and usually in small amounts, which probably fail to produce sufficient focal stimulation to overcome the mechanical hindrances of the more advanced pathological process which has developed; and in this way, fail to induce a sufficient immunizing response and fail to produce the focal stimulation necessary to bring about a cure.

Tuberculin, however, when injected artificially, has these advantages: first, that it is injected into cells which are not directly injured by the tuberculous process and where the powers of response are probably better; and second, it is injected in doses which can be controlled and which can be administered often and in sufficient amounts to produce the necessary focal reaction, thus producing the natural inflammation which is necessary to healing. Whether this is the true explanation or not, it is in line with our theories of healing; and the fact that the artificial administration of tuberculin produces healing where nature fails is in accordance with our clinical observation.

Autotuberculin Therapy.—In our endeavor to cure the various infections, notably those of a progressive nature, it has been shown that autogenous vaccines seem to have a more favorable effect than vaccines made from stock cultures; therefore it has seemed to many that, if it were possible to treat a patient artificially with tuberculin from cultures of his own tubercle bacilli, we might obtain more satisfactory results. It is very probable that tubercle bacilli as they grow in the tissues are somewhat different from those that grow in the laboratory upon artificial media, and that the toxins given off by them may be somewhat

different as they are produced in the natural infection and in the laboratory. It is also probable that the specific action of those toxins which escape from the focus of infection from the patient's own bacilli are somewhat different from those of the tuberculin which we have produced artificially. On this account there have been attempts to grow bacilli from the patient's own sputum and treat him with tuberculin from his own bacilli; but this causes no end of labor and a great loss of time, which makes it impracticable.

In this connection, however, if the theory which we have accepted as to the action of tuberculin is correct, every patient is treated partly, at least, by his own tuberculin. It is not only the tuberculin which is injected into the tissues that is brought into therapeutic application in the case but that which comes from the destruction of his own bacilli. Through the increase of lysins, produced by the stimulation of the tuberculin as introduced, the body is so thoroughly guarded that, whenever tubercle bacilli escape from the focus of infection, they are destroyed, and their own natural toxins liberated to be used in producing their specific action in healing. Whether we could gain anything beyond this from treating with cultures from the individual patient, we are not able to say. In this connection it must be remembered that when the culture is taken from the individual patient and grown on artificial media the resulting tuberculin would be at least to a certain degree subject to the same criticism as the tuberculin which is usually produced in the laboratory. It would be made from bacilli grown on foreign media, and whether the fact that they were only one generation removed from their natural host would mean much to their advantage is open to question.

The experiments of Paterson, [10] at Frimley, represent a definite attempt to treat patients with autoinoculation. His method is to control the amount of tubercle toxins absorbed by the bloodstream from the focus of infection. This he aims to do by suiting to each patient the amount of work which will induce the proper autoinoculation. His work is a monument to his patience and perseverance and sheds light upon the immunizing response which follows the natural course of tuberculosis. As a method of treatment, I can, as yet, see no advantage in it over the hypo-

[10] Autoinoculation in Pulmonary Tuberculosis, London, 1911.

dermic method of applying tuberculin, except that the patient receives in his autoinoculation the exact constituents which nature has provided for cure, consisting not of tuberculin alone, but enzymes, cellular elements, etc. The disadvantage is the fact that treatment is limited largely to simple cases, the more extensive ones being ruled out.

Negative Phase.—After Wright's work on opsonins had become known to the profession, the entire medical world became thoroughly imbued with his idea of the "negative phase"; and everybody feared it in tuberculin therapy. That this negative phase exists, as is shown by the opsonic record of patients treated for tuberculosis, there can be no question. That it is as serious clinically as we have been led to believe is open to question, because nearly all the treatment of tuberculosis that has occurred throughout the world has been carried on without reference to the "negative phase." The results obtained before the negative phase was recognized seem to be about the same as the results obtained today, except as men are becoming more proficient by long experience in the use of tuberculin.

In my practice I have always disregarded the laboratory determination of the negative phase and given my doses according to the method which produced clinical results; and this has given me a very satisfactory degree of success in therapy. Formerly I started my patients with daily injections of tuberculin, increasing the dose each time until I reached a dose of moderate size. Then I administered the remedy every second day, later every third day, etc., increasing the intervals as the size of the dose increased. According to the principles laid down since observing the negative phase, I must have had my patients in the negative phase all the time; but if I did, it was of no serious consequence, because my patients made clinical improvement coincident with the injections. It is possible that after repeated injections of the tuberculin in close succession, as we used it at that time, the negative phase becomes inconsequential. It is also possible that these small doses with which we began our administration produce a negative phase so slight that it is negligible, or one that passes off very rapidly within a few hours before the next dose is administered; but however that may be, we know from clinical experience that the negative phase has not seemed to interfere with good clinical re-

sults. In saying this I do not wish in any way to detract from the great work which Wright has done. I consider him one of the greatest men in modern medicine, but I wish to take away the inordinate fear of the negative phase which seems to be in the minds of some men who are attempting to use tuberculin. It seems but rational to suppose that, if the body contains a certain amount of antibodies, and a certain amount of toxin for which these antibodies have a specific combining affinity is injected, a certain proportion of the antibodies will be used up, and there will be a temporary decrease in the defense of the organism. But there is another principle in immunity which must be considered: namely, that the specific toxins stimulate the cells at once to the production of a far greater number of specific antibodies than is necessary to neutralize or satisfy the toxin injected; consequently the body is left with an increased supply of new antibodies after its equilibrium has been restored. This being true, it is probable that, in the use of tuberculin, we so increase the immune bodies present that the injection of our tuberculin uses up such a comparatively few antibodies that the temporary diminution of them is inconsequential; and further, it is not beyond reason to suppose that one dose of tuberculin might be using up antibodies, while the preceding one is stimulating the cells to the production of new ones.

Whatever the explanation may be, we may safely administer therapeutic doses of tuberculin, relying entirely on the clinical symptoms and the progress of the patient without reference to the estimation of the negative phase by laboratory methods.

Tuberculin Difficult of Administration.—No one who has had extended experience in the use of tuberculin will declare that it is easy of administration. Anyone can draw up a certain amount of a certain solution of tuberculin into a syringe and inject it under the skin, but that is not treating tuberculosis. To adapt the dose to the condition present is a very difficult procedure. To know just when to increase, how much to increase, to know when to withhold the dose, to know when to give it, can be obtained only after long and careful study of the remedy and the disease. This does not mean that tuberculin cannot be administered with a fair degree of success without great experience, but it means that, to get the best out of tuberculin, and to do the patient the most good, experience is indispensable. In this, tu-

berculin is like everything else. The first operation that one performs for appendicitis is not a record operation; neither is the first case of typhoid fever usually treated so well as those after a certain experience has been gained.

In spite of the difficulties that exist and in spite of the fact that I firmly believe that routine should not be followed in the administration of tuberculin, yet I am sure that its administration can be learned sufficiently well with a moderate amount of careful study so that any intelligent physician can employ the remedy to the advantage of the patient. The man who is beginning, who has had very little experience in either the use of tuberculin or the general treatment of tuberculosis, must be slow to give his opinion as to its value. He must of necessity take a great deal for granted. It will be impossible for him to give an intelligent opinion from his experience; but if he will follow the general rules which have been formulated by others from a study of the remedy and the disease, he will do no harm, and will, after a little time, gradually see wherein he is aiding the patient and wherein he is helping to bring about a cure; or, if he is making errors, he will see the source of error.

In spite of the fact that I am discussing the principles of tuberculin therapy in this monograph, hoping that it may be a guide to many practitioners in the administration of tuberculin, yet I would earnestly urge and advise that all who are intending to administer tuberculin in the treatment of tuberculosis first study the employment of the remedy, if at all possible, with some man who has had experience in its use. Before a man starts surgery, he goes where he may see surgeons operate. Before a man undertakes to treat most diseases, he studies and observes other clinicians in their handling of these various cases. So it should be in tuberculin therapy, remembering that tuberculin is a double-edged sword that can cut either way. It may either do great good or great harm, according to whether it is used rightly or wrongly. Therefore, if a physician intends to administer tuberculin, if it is at all possible, he should first learn by observing its administration by some one who knows.

Length of Time of Treatment.—The length of time necessary to carry on treatment for tuberculosis will always militate against its cure. It is a very difficult thing to obtain the co-operation of the patient, and it is likewise very difficult for most

physicians to keep up their interest in the patient during the prolonged period of months or years that is necessary to bring about a cure in this disease. But unless a physician can keep up interest in a patient throughout a prolonged period of time and be willing to be his adviser and counselor, even in what might seem to be trifles, as well as in big undertakings, he is not fitted for treating tuberculosis and should let tuberculin therapy alone. The administration of tuberculin adds greatly to the interest in the case because it compels a close watch of the patient and aids in a more thorough co-operation between patient and physician. It brings the physician and patient together more often, and in this way tuberculin has probably increased the chances of cure in patients suffering from tuberculosis more than we realize.

The length of time of tuberculin treatment in nowise differs from the length of treatment of tuberculosis in general. It is treatment until the best possible result has been obtained. One point that I would like to emphasize is that the tuberculin treatment of tuberculosis is coextensive in point of time with the treatment of the disease itself. While I recognize that it is not always desirable or necessary to keep up tuberculin continuously during the entire period that the patient is recovering from tuberculosis, at the same time the patient should be treated with tuberculin from the time the disease is discovered until the best result possible is obtained, although periods of rest from tuberculin may be desirable at times. Patients who have obtained a good result from treatment usually profit greatly by taking injections for two or three months again, beginning from six months to a year after the injections have ceased and then again after the lapse of six months more. This tends to make healing more complete.

The expression "a course of tuberculin treatment," as it is usually employed, gives a wrong impression. There is no set course of tuberculin treatment. This expression is ordinarily used to mean the time necessary to arrive at a certain dosage, given according to some special rule. Inasmuch as there is no maximum for all patients, the maximum for one patient being very different from that of another, it can at once be seen that it is wrong to speak of a "course of tuberculin treatment," meaning any special length of time or the attainment of any definite maximum dose.

There are numbers of men who are so thoroughly committed to the tuberculin treatment that they do not believe that a patient is being properly treated for tuberculosis unless tuberculin is being employed; and I personally feel that I would not be doing my patients justice unless I gave them the benefit that I have learned to give by the employment of tuberculin. On the other hand, there are men who have no faith in its employment, who feel that they can do just as well for their patients without its use as with it. When such a man determines to give tuberculin a trial, as often occurs, he usually begins with a biased mind, has only a half-hearted interest in the trial, and as a rule, comes out at the end convinced that he was correct in his former estimation. The man who endeavors to test tuberculin in such a manner today finds the experience of hundreds of able clinicians against him. He should not start with the purpose of testing tuberculin. It has already been tested. He should start rather with the idea of testing his own ability to administer tuberculin. He may fail, but he must not lay the failure to the remedy.

Indications and Contraindications for the Use of Tuberculin.—I am somewhat at a loss to understand just what is meant by indications and contraindications to the employment of tuberculin as laid down by many writers. I cannot understand their point of view. Our opinion of the indications for the employment of tuberculin must necessarily rest upon our ideas of what tuberculin will do. Those of us who are most enthusiastic in its use, and yet who understand thoroughly its shortcomings, but who are willing to accept any possible good that can be derived from its employment, use it much more extensively than those who seem to be convinced to a less degree of its value. The disappointment which some feel is due to the fact that they expect too much of it.

In my idea of the indications for tuberculin, I am guided by my understanding of nature's method of cure. In the natural treatment of tuberculous infection, the specific toxins which call the machinery of immunization into action and stimulate the foci of infection to healing begin to be thrown out as soon as infection takes place, and they never cease until the cure or the destruction of the patient occurs. To be sure they often fail to bring about cure, but nature does not stop their production because of

this failure. From my study of tuberculin and tuberculosis, and from my clinical knowledge of its action, I can see no more reason for stopping the use of tuberculin in those cases which are usually classed as "unfavorable" for tuberculin therapy than I can for stopping fresh air, good food, or carefully regulating the life of the patient. To be sure I do not expect to obtain so good results in the advanced cases, especially active cases, as I do in the early ones, but I expect to give my patients the benefit that I know, from experience, tuberculin is able to produce. Any good, no matter how small, is welcome. I have been led to these opinions by trying to produce the best possible result in private patients.

Early Treatment.—I cannot urge too strongly the early treatment of tuberculosis, for I feel that we have been very remiss in our treatment of this disease. We have been so afraid that we would do the patient an injustice by putting him on treatment early, feeling that he might possibly get well if left alone, that we have erred on the side which has often proved to be a great injustice to him. I firmly believe that in the not very far distant future we shall be taking as advanced a stand on tuberculosis as the surgeon is on appendicitis and gall-bladder diseases, and as the general physician is on syphilis and practically all other diseases with which he has to deal. That is, we shall be recognizing that the earliest possible time when we can find active symptoms in tuberculosis is the time that it demands our attention and intelligent treatment. We shall recognize the fact that latent tuberculosis is not healed tuberculosis and shall also further recognize that the treatment of the patient during the period of latent tuberculosis means cure in nearly every instance. The surgeon does not wait to be sure that the patient is going to have a fatal attack of appendicitis, or a fatal attack of gallstones; neither does he wait for a growth that is suspicious of cancer to go on to the inoperable point, nor does the physician wait for latent syphilis to become active, before instituting proper treatment. He tells the patient that he has appendicitis, or gallstones, or that he has a growth that is suspicious of cancer, or that he has syphilis, and that the very best treatment that science knows is to eradicate it before it becomes serious. The result is that the early operation for appendicitis, gall-bladder diseases, and cancer in the quiescent stage produces cure except

in cancer, in nearly all instances without injuring the patient. The early treatment of syphilis relieves the patient and saves him from further trouble. Now, why not treat tuberculosis with the same judgment, the same fairness, and in the same scientific manner, and prevent these latent lesions from becoming active clinical tuberculosis? To be sure, if we do this, we shall treat some patients who might get well of their own accord, but we shall treat them at a time and in a manner that will not make it necessary for them to quit their ordinary vocation. They will be put to less expense and less inconvenience than in any other way, and they will be relieved of a great danger with which they will otherwise always be threatened. In this connection we must admit that we have no way of telling which ones will become active and which ones will not. A bomb with a lighted fuse under a house is always a danger. While the fuse might go out of its own accord, we should not take the risk of its doing so. It is just as important and it is no nearer a crime to treat a patient who is suffering from an unhealed though quiescent tuberculous lesion than it is to operate on a patient for appendicitis when no activity is present because he has had a previous attack.

Tuberculin Active Immunizer.—Tuberculin treatment is active immunization, and this throws a certain amount of work upon the body cells which requires of them a power of response. If a patient's vitality is very much lowered, we must not expect so good a response as we would in case the patient were in better physical condition. Such a patient, however, will not respond as well to open air, good food, constant care, and careful guidance as those in good physical condition; but would we withhold these from him because of it? Such a patient will not respond so well to the stimulation produced by the toxins coming from his own focus of infection; but does nature stop the toxins on account of this? We must not expect such a patient to respond with the production of so many antibodies as though the cells were perfectly normal, nor must we expect the stimulation in the focus of infection to yield so great healing effects as though the lesion were less extensive and the patient were in better condition; at the same time, it is just as essential to give this patient what chance we can by the administration of tuberculin as it is by the administration of any other remedy.

Rapidly Progressive Cases.—Rapidly progressive cases of tuberculosis are said to be unfavorable for tuberculin therapy. They are unfavorable for all therapy; nevertheless I have treated numbers of cases of this kind, and by being satisfied with the help that I could bring and persisting in the application of every remedial measure that was at my command, I have been able to obtain some excellent results in this type; and in those advanced cases which are always said to be unfavorable, where there are extensive destructive processes going on, the same statement applies.

I will mention one very interesting case history illustrating this point:

The patient was a young man twenty-one years of age, suffering from an acute caseous tuberculous process of the entire upper lobe of the left side, with scattered tubercles throughout the entire lower lobe and the upper portion of the right lung. Temperature from 102° to 104°, of the inverse type. Patient had lost much weight, suffered severely from the toxins, and was rapidly failing. This would be considered a most unfavorable form for tuberculin treatment. I consider this a most unfavorable form for any kind of treatment.

This patient was put in bed, however, and kept there for about nine months. The daily maximum temperature varied from 100° to 104° during the first four and a half months, then gradually became lower. The expectoration and cough became more profuse at first, and the patient formed cavities in the upper lobe; in fact, the upper lobe was practically all excavated. In the lower lobe healing occurred; and while some cavities formed, contraction took place, and these gave little trouble. The disease in the right lung healed entirely except a small focus at the right base which was due to an extension at that point.

The pathological condition in the left lung became quiescent, all symptoms ameliorated, the patient regained his full weight, and looked and felt well. His sputum gradually decreased from 140 cubic centimeters, the greatest amount, to 25 cubic centimeters a day. The temperature curve had been running practically normal for about four months, and the pulse was only a little above normal when the patient was taken with a severe hemorrhage which proved fatal. An interesting fact about the hemorrhage was that the patient would bleed until the cavities w

filled. The pressure from the clot closed the opening in the vessel, stopping the hemorrhage for the time. After two or three days the clot would soften and come away, and a new hemorrhage would occur. This continued for six weeks before death. Compression of the thorax, while indicated, could not be done on account of the thickened adherent pleura.

On post mortem we found that the upper lobe on the left side consisted of a shell of lung surrounding two large cavities. The lower lobe on the left side was a firm fibrous mass of scar tissue, with a few small cavities. The left lung was not functionating at all. The right lung was enlarged, pushed over beyond the median line, and was apparently healed except at the base where there had been an extension which had produced a small tuberculous necrotic focus, very limited in extent. The cause of death was an opening in a vessel running across the upper cavity which had failed to become obliterated. This patient was under treatment, including tuberculin, from the time I first saw him until his death, twelve months in all; and while some of those who oppose the use of tuberculin under such circumstances might say that it was contraindicated in such a case and that he improved in spite of it, I, who treated the case, am firmly convinced that his great improvement was largely aided by the artificial administration of this specific remedy. His death was purely accidental. Had nature closed off the vessel when the cavity formed, he would probably have lived many years. This case is only one of many that I might mention.

One very important observation in this case, and one which we often note, is the fact that while serious breaking down was occurring in the left lung, healing was taking place in the right, and before the temperature had reached normal the right lung was practically clear of active disease. Tuberculin must be given part of the credit for this result.

Indiscriminate Treatment Not Favored.—Lest it should be gathered from what I have just written that I favor the indiscriminate treatment of tuberculosis with tuberculin, I would like to correct such an impression before going farther. I am sure, if those who have not had experience in tuberculin were to undertake to treat such advanced cases as this, that tuberculin would rapidly fall into disrepute. The object of this monograph is to help tuberculin and the tuberculous patient, not to harm

either of them; to show what tuberculin will do, at the same time to teach what it cannot do. I would especially caution those who are not conversant with tuberculin therapy, or those who have only a limited experience, that they be most careful in choosing patients for treatment. Simple cases do not only offer better opportunity for obtaining a favorable result, but it is easier for the physician to appreciate the favorable changes which result. In advanced cases the pathology is so complex, the clinical course is so uneven, that it is almost impossible for a man without experience to differentiate between the effects of the remedy and the natural course of the disease. It is necessary to avoid such cases until one is thoroughly conversant with the action of the remedy.

Owing to the specific nature of the focal reaction, it can also be seen that it is more easy to harm where there is a widespread disease with marked activity than it is in a simple lesion, such as is present in early tuberculosis. I would therefore emphasize that those who have not had much experience in treating tuberculosis and in the employment of tuberculin, and those who are not in a position to control their patients thoroughly, and especially those who are using tuberculin for the first time, be most careful in the selection of patients. I would advise that they treat no fever cases, and that only patients be taken whose temperature is running less than 100° and such as are not subject to frequent rises of temperature due to increased activity in the lung.

Not only would I advise patients who are fever free, but I would advise that the lesion be a favorable one, that the patient be one suffering from either an incipient lesion where only a small amount of involvement is present, or, if the case be a chronic one, that it be either one of the fibroid type, or at least one where the activity is practically nil. I would also suggest that clinical symptoms be looked into carefully and that such a patient be chosen who offers good resistance to the toxins. I would also suggest that a patient be chosen who is free from serious complications, of either a non-tuberculous or tuberculous character. If such a method is followed and the remedy be applied intelligently, tuberculin cannot fall into disrepute, for none but good results will follow.

Mixed Infection.—Mixed infection is usually given as a con-

traindication to tuberculin treatment. What I have said regarding these other advanced forms will also apply to this. The use of tuberculin in fever I shall discuss elsewhere (pages 202–211), but I desire to say here that I do not consider fever a contraindication for one who understands how to use tuberculin. For the beginner it is a contraindication; and one with little experience had better not undertake to treat fever cases.

Hemorrhage.—Hemorrhage is very often given as a contraindication to the use of tuberculin. I can see no reason why tuberculin should not be employed in hemorrhage cases. Some authorities, notably C. Spengler, even suggest that the proper treatment of hemorrhage, due to a ruptured vessel, is a dose of tuberculin, believing that the focal reaction produced in the tubercle will aid in closing off the break. I, personally, always stop injections during hemorrhage and wait until color has entirely disappeared from the sputum for several days before resuming the administration. Hemorrhage cases, however, are as well suited to tuberculin therapy as any other cases.

Rapid Pulse.—There is one symptom which is usually given as a contraindication for tuberculin treatment, which, to my mind, should certainly not be considered: that is, the persistently rapid pulse. It is no more a contraindication for tuberculin treatment than it is for other treatment. One of the general statements that has been made with reference to tuberculosis for many years is that patients with rapid pulse are unfavorable for treatment, and this has caused many a physician to throw up his hands and lose hope when a rapid pulse was found. I wish this impression could be overcome. I, personally, have seen good results in patients who had a rapid pulse for many months sufficiently often to disprove this statement. Like so many other general statements, it works no good. On the other hand, it does great harm to the therapeutics of this disease. I recognize that the persistently rapid pulse is an undesirable complication; at the same time it yields to appropriate treatment the same as other symptoms, and I protest against condemning a man to death because he has tuberculosis and a persistently rapid pulse. Fig. 4 shows pulse and temperature tracings of a patient given up to die with acute disseminated tuberculosis of both lungs. The patient is now free from fever, without cough and expectoration, and rapidly gaining in strength and general health.

The persistently rapid pulse may be due to many different causes. We sometimes find it due to the effect of the toxins. Such cases should be particularly favorably influenced by tuberculin therapy. At other times it is associated with an enlarged thyroid. I have seen several cases of this kind and could see no harm from the tuberculin used. Then, it must be remembered that anything that will stimulate the cardiac sympathetics or interfere with the action of the vagus will produce rapid heart action. It also represents a response on the part of the heart to

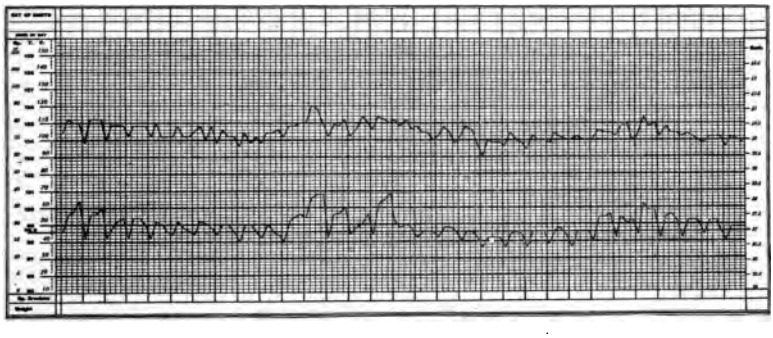


Fig. 4.—Illustrating a case of tuberculosis accompanied by rapid pulse, the patient making satisfactory improvement. The patient suffered from a disseminated tuberculosis of both lungs, which went on to an arrestment. The curve also illustrates the waves of activity in the disease, the temperature being up a few days, then down for a few days, and then up again, etc.

maintain blood-pressure and to favor the proper oxygenation of the blood when the lung capacity is lessened. It also often occurs when the heart is pushed out of place by contraction. Aside from these, overeating, intestinal toxemia, nervousness, and innumerable other factors operate to increase the pulse rate, but I cannot see a single one of them which will warrant the assertion that a rapid pulse is a contraindication to the use of tuberculin, unless all difficult cases are to be excluded from the benefits of tuberculin.

Organic and Constitutional Diseases.—Severe organic and constitutional diseases have also been mentioned, such as heart disease, which is rarely found in conjunction with tuberculosis, nephritis, and diabetes; but I must insist again that our classifying these as contraindications is due to our failure to appreciate just what tuberculin will do, and our failure to be satisfied with the best that we can obtain from its administration. In order

to consider a remedy as indicated, it is not necessary that its use guarantees a cure. In diabetes, instead of finding it a contraindication, I believe tuberculin is a measure of great value. I have had two cases of diabetes which completely lost their sugar during the course of treatment. It might be that sugar in these cases was increased by the toxemia, and the reduction of the toxemia by the treatment relieved it, but whatever the explanation is, the result is very interesting and suggestive. I have also treated patients with organic heart disease and nephritis and have seen no harm result. On the other hand, I have seen the patient benefited as the pulmonary condition improved.

When we realize the value of tuberculin in relieving many of the symptoms that are present in these cases, I do not see how we can say that it is contraindicated. If it will lessen the cough, if it will decrease the toxemia, if it will increase the patient's general nervous tone, if it will help to fortify the patient against further extension of the disease, if it will help clear up the various complications that are present, it would seem to me that, instead of being contraindicated, it is most positively indicated; and so have I found it in my practice.

I would not suggest that those who are using tuberculin under less favorable circumstances than I am, or those who have had little experience in its use, be as free in its employment as I, but I have made it a rule for several years to employ tuberculin in nearly every patient that comes under my care. I have watched my patients carefully. They have been under my constant supervision in the sanatorium, where I have seen them daily, and I have seen nothing but the happiest results follow its administration. I have seen improvement, arrestment, and even healing occur in many cases which have been considered absolutely hopeless by the physicians referring them for treatment.

I do not wish to be considered as a special pleader for tuberculin. It does not need any special pleading. Its action is so well established by so many able clinicians that it pleads its own case. Neither am I pleading for its use in these advanced cases, but I wish to be distinctly understood as believing that tuberculin, properly administered in these advanced cases, is valuable and not harmful. I further hope to make it plain that tuberculin is not contraindicated in advanced tuberculosis and in the various conditions that are usually considered grave; but I wish to

emphasize it just as strongly that the treatment of these severe complications should not be carried on by men of little experience. This work must be left to men of experience who can give the patients the benefit of ripened judgment. Neither must the remedy be expected to perform miracles in these cases. Any good resulting must be welcomed, and if none comes, the remedy must not be blamed any more than an operation is blamed for not curing incurable cancer.

CHAPTER VII.

HYPERSENSITIVENESS.

In modern studies of immunity a certain phenomenon has been discovered which deserves special attention. It is the specific change, the specific hypersensitiveness in the tissues, which occurs after an organism has once been inoculated with a foreign protein. Whether general or bacterial protein, the phenomena are the same. Von Pirquet chose to call this condition "allergy." His conception is explained elsewhere in the monograph (page 29). Wolff-Eisner,[1] who has carefully studied hypersensitiveness, defines the condition thus:

"By *hypersensitiveness* is meant the condition of an organism upon which an excitant has acted one or more times, the organism reacting more strongly at each repetition of the excitant than does another organism of the same kind upon which the same excitant is acting for the *first* time. To merit the term 'hypersensitiveness,' the difference in reaction must be so obvious that it cannot be ascribed to individual conditions of hypersensitiveness."

And again:

"A hypersensitiveness occurs after the injection of a heterogeneous albuminous substance (serum, albumin of an organ, or bacterial albumin) and becomes manifest on repetition of the injections."

It will thus be seen that, according to Wolff-Eisner's theory, the specific cause of hypersensitiveness is not the toxin as such, but the specific protein, the bacterial albumin. The hypersensitiveness found in tuberculosis is of the same nature as that produced by the injection of any other albumin and only differs in that it is produced by the protein from the tubercle bacillus. This theory is rapidly gaining ground as affording a rational explanation for the phenomena which are met. It will be remembered that, when discussing the nature of the tuberculin

[1] Clinical Immunity and Sero-Diagnosis. Wm. Wood & Company, p. 37.

reaction, I mentioned that Wolff-Eisner considers all tuberculins as being the same qualitatively and differing only quantitatively, thus differing only in the amount of specific protein which they contain. He would explain the hypersensitiveness produced by the natural tuberculous infection as being due to the action upon the body cells of the protein which escapes from the infecting bacilli.

Van Calcar[2] expresses the belief that hypersensitiveness is only the ordinary precipitation reaction. He states that, if a given animal is injected intravenously with a given quantity of protein, by the aid of the precipitation reaction it can be shown that the protein circulates freely in the blood for a time, showing that the various organs have no affinity for it. Gradually, however, it combines with the cells, and they in turn produce antibodies as a result of irritation. These antibodies remain partly bound to the cells which produce them and partly circulating in the blood-stream.

The first observation of specific hypersensitiveness was that of Koch when he observed the difference in the action between a guinea pig which was already tuberculous and again infected by tubercle bacilli by subcutaneous inoculation, and a guinea pig which received its inoculation for the first time. When the pig is inoculated a second time an infection does not occur, but there is a specific reaction at the point of inoculation. The tissues break down immediately, forming an ulcer. This is probably the result of a local specific hypersensitive reaction which takes place between the bacilli and the specific antibodies of the tissues. There is an attempt to destroy the bacilli and ward off infection. Where the pig has not received a previous inoculation, however, there is no attempt of this kind; hypersensitiveness is not present, and the bacilli are left free to produce infection except as they are opposed by the natural defenses of the body, which are probably not specific.

While Koch made the first observation of hypersensitiveness, it was von Behring[3] who first used the word in its present sense.

Römer,[4] after many careful experiments, determined definitely that hypersensitiveness was a phase of immunity. Previous to

[2] Tuberculose und Immunität, 1910.

[3] Die Gewinnung der Blutantitoxine und die Klassifizierung der Heilbestrebungen bei ansteckenden Krankheiten, *Deutsche medizinische Wochenschrift*, 1893, No. 48.

[4] Spezifische Überempfindlichkeit und Tuberkulose Immunität, *Brauer's Beiträge zur Tuberkulose*, vol. 11, 1909.

the studies of such investigators as von Pirquet, Wolff-Eisner, and Römer, we were inclined to look upon hypersensitiveness as something very undesirable. We did not recognize it as a phase of immunity. We only knew it as we occasionally found it, as a hypersensitiveness to tuberculin, in the therapeutic use of this remedy.

We now understand it, however, to be an agency of defense, indicating that the organism has been previously attacked by a certain enemy and that it is now on the lookout, so to speak, for attacks by the same enemy, and ready to respond in its destruction.

While hypersensitiveness is a necessary and desirable condition in tuberculosis, being a reaction which indicates the presence of a degree of immunity, in our therapeutic employment of tuberculin, patients sometimes develop a hypersensitiveness to tuberculin which is very annoying, and which, if we desire to carry out tuberculin therapy to advantage, must be avoided as much as possible. The writer had one very marked case of hypersensitiveness to tuberculin to deal with early in his experience with tuberculin therapy. It was most annoying and caused him a great deal of concern. A patient who had been able to take quite large doses of tuberculin suddenly developed such a sensitiveness to the remedy that the minutest dose produced a reaction. While he had been able to tolerate 750 milligrams of von Ruck's Watery Extract of Tubercle Bacilli, after this condition appeared he could not tolerate a milligram, and after such injections reacted with high temperature. This was at a time when nothing was known of specific hypersensitiveness, and I was utterly unable to offer an explanation of the phenomenon. I stopped injections for about a month and began with a minute dose again, when the patient showed another reaction. I then waited a few weeks longer, after which time I was able to take up the treatment without difficulty. In another very marked case, after the patient had reached the point where she tolerated quite large doses of human tuberculin, she developed a hypersensitiveness and reacted each time an injection was given, no matter how small. I overcame this without stopping the injections by changing to another form of tuberculin. By giving bovine tuberculin, I was able to proceed with my therapy without difficulty. This experience is difficult to explain in the

light of Wolff-Eisner's theory of all tuberculins being the same qualitatively, although much confirmatory evidence seems to be found favoring his theory. I would call attention to the fact, however, that several different proteins have been isolated from the tubercle bacillus and that the difference might be explained on the ground that one preparation contains more of a given protein than the other; and that this case of hypersensitiveness was due to certain proteins in the human preparation which the bovine product did not contain, or at least not to so large a degree. It is also known that different media produce bacilli which differ in form and virulence. Might it not be that the specific proteins of the bacillus when grown on different media differ in quantity or probably even in quality?

Having been a pioneer in tuberculin therapy, I have received many letters from physicians asking me to help them in their difficulties, and one of the most common troubles is that the patient has become hypersensitive to the remedy. I believe that this is due to the method of administration and that it can be overcome by care.

I have not had a single case of hypersensitiveness to tuberculin develop in my own practice during the past seven years, although I have treated several hundred patients during that time. I have had, however, numerous patients that had been treated by others that were hypersensitive. This condition is best overcome by changing the preparation used.

I believe that the same principle holds good in tuberculin protein as in other proteins. We have learned that experimental serum diseases (hypersensitiveness or anaphylaxis) may be produced by the inoculation of small doses of serum at infrequent intervals, but that this serum disease may be prevented by injecting increasing doses at short intervals. I believe that this same principle applies to tuberculin therapy. The dose of tuberculin following the first should be rapidly increased with short intervals. It seems to me that the probable reason that we do not get a hypersensitive reaction more often in the therapeutic employment of tuberculin is because our patients have been rendered somewhat insensitive by the doses of bacillary protein which they have given themselves from their own foci of infection from time to time. When infection occurs the probabilities are that doses of tubercle protein are given out in rapid

succession, probably almost constantly, so that, instead of a condition of marked hypersensitiveness developing, a condition of insensitiveness occurs. This condition of tolerance having been attained, a hypersensitive reaction does not occur when the protein inoculation, represented by the usual doses of tuberculin injected therapeutically, is made.

This phase of hypersensitiveness (hypersensitiveness or intolerance to tuberculin) must not be confused with the hypersensitiveness represented by the changed condition of the body cells, resulting from an infection, although it is probably only a different phase of the same condition. The principle of hypersensitiveness to protein is given so well by Wolff-Eisner[5] that I will quote him. Speaking of the symptoms of serum disease he says:

"Although they may be forced by high initial doses, in cases where small doses are used, they occur in practically one hundred per cent, after the fourth or fifth injection, provided, of course, that the injections do not immediately follow each other, but succeed at intervals of not less than eight or nine days, corresponding to the period of incubation in serum disease, during which the antibodies are formed, without which serum disease cannot occur. There is, of course, no absolute insensitiveness to a heterogeneous serum that may not be overcome by increasing the dose; much less is insensitiveness acquired. On the contrary, there arises a hypersensitiveness, as after the injection of any heterogeneous albumin characterized by increased or accelerated reaction symptoms, *or by the occurrence of the same reactions after either small or large doses.*"

This describes the same condition that occurs when we meet a hypersensitiveness in our therapeutic administration of tuberculin. The patient arrives at a place that, no matter what injections be given, whether large or small, a reaction occurs. This hypersensitiveness occurs most often when the remedy is not given correctly. I believe that whether or not we are going to be bothered by this condition is determined in most instances by the way the injections are started. If small doses are used in the beginning and they are increased slowly, with long pauses between them, the exact condition is present which favors hypersensitiveness (serum disease). If, on the other hand, we begin with small doses, and with short intervals, increase our doses

[5] Immunity and Sero-Diagnosis, p. 42, William Wood & Co., 1912.

rapidly, we are taking the course which in our treatment prevents hypersensitiveness (serum disease).

In order to avoid this undesirable complication, I would suggest that when a patient is to be treated with tuberculin extreme care be used in the beginning of treatment. I do not mean by extreme care that small doses be used, and that they be given at infrequent intervals, but just the contrary, remembering that hypersensitiveness is favored by small doses infrequently given. I would urge that a patient be started with a small dose and that, with short intervals, the dose be pushed quite rapidly, of course, always avoiding reactions. I usually make my first dose so small that the second dose can be ten times as large and the third, one hundred times as large without danger of producing reaction. It will soon be learned that, if this rapid rise in dosage is employed in the beginning of treatment, the danger of reactions is much less than where the dose is increased more slowly. It will also be learned that short intervals between doses lessen the danger of reaction.

If a condition of hypersensitiveness should happen to develop in spite of the rules which I have laid down, I would suggest that the treatment be continued by some other tuberculin, thus using a different protein or a protein which has grown on different media. This will probably make sufficient change to overcome the hypersensitiveness. I would further suggest that the patient be started with the initial dose for the preparation used, disregarding the fact that a particular-sized dose had already been attained before the hypersensitiveness developed.

CHAPTER VIII.

CERTAIN CONDITIONS WHICH HAVE MADE THE ADOPTION OF TUBERCULIN AS A DIAGNOSTIC AND THERAPEUTIC MEASURE DIFFICULT.

The Disaster of 1890-91.—In order to fully appreciate the injustice of the prejudice which tuberculin has been obliged to overcome, it is necessary for us to refer to the early trial of this remedy in the early nineties. The first trial of tuberculin was a very unfortunate one. Koch had done his work and had obtained absolute proof that the remedy had curative properties. He had followed the healing of tuberculous foci as a result of its use in animals. He had also seen human beings suffering from early tuberculosis lose their clinical symptoms and recover their health, aided by its administration. He had also laid down certain definite rules for the administration of the remedy. These rules were based upon his own study and experience. To be sure, he was in a new field and had nothing to guide him; but with all that against him he had worked out the problem in such a manner as to be able to produce healing in a disease which had hitherto baffled medical skill and he had observed so closely that the rules which he laid down at that time are, with a few modifications, the guiding principles of tuberculin therapy today. While they have been altered by more extended clinical experience, yet the principles have been largely maintained. (See Appendix for translations of Koch's papers in full.)

These are a few of the observations and rules that Koch published in his first paper:

1. Early cases are most suitable for treatment and can be cured.

2. Advanced cases can be helped, but the improvement takes place very slowly. Those without complications are most suitable.

3. Widespread disease, such as is found in the lung, reacts to

smaller doses than localized lesions; consequently the beginning dose should be small.

4. Begin with small dose, and if reaction occurs, repeat dose until it fails to produce reactions.

5. As the injections continue, larger and larger doses will be necessary to produce reactions.

6. As noticed in lupus the reaction should be allowed to pass off before the dose is repeated.

7. In cases beyond the earliest stage all other measures known to medical science must be used to aid the remedy.

8. The remedy must not be used in a routine manner but adapted to each individual.

That his rules were not followed can readily be seen by reading the literature of that period. Patients were treated with tuberculin who were in the late stage of tuberculosis and who were within a few weeks of death. It seemed that no one was denied the remedy, no matter what the stage of his disease, in spite of the fact that the remedy was on trial. This would not have been so serious a matter, however, had it not been that new observations were being made. Tuberculosis was being watched both clinically and pathologically, as it had never been before, and not altogether by friendly eyes either. Every new unfavorable observation was attributed to the remedy whether produced by it or not. The same rules which were laid down for the treatment of early cases were also followed for late cases. No discrimination was made. Individualization was not thought of. The result was that the cases of improvement that resulted were lost sight of in the great amount of harm that was done to others. Koch himself reported on 150 cases which he observed, with satisfactory results.

The blow to tuberculin would not have been so serious had the remedy not been heralded world wide. Everybody knew of tuberculin; consequently everybody knew of the harm that it was doing, and everybody knew that it had failed to be the magic cure for tuberculosis that had long been looked for and was hoped for when it was announced. In consequence of this great disappointment the progress which tuberculin has made toward recognition as a measure of diagnostic and therapeutic worth has been against the will of a hostile profession and a public which had trusted and been deceived.

Probably one of the severest blows to tuberculin was the pathological findings which were made by Virchow. Virchow found that certain things occur. He found that miliary tubercles were present in the lungs of patients who died of tuberculosis after treatment with tuberculin; therefore the idea was suggested that tuberculin mobilized bacilli which had previously been shut up in the tuberculous foci and in that way caused dissemination and a miliary condition. Virchow did not say that the same thing is not found when patients are not treated with tuberculin. The minute changes in the lung had not been studied before and so it was not known. This, however, was soon demonstrated by Petruschky. While this "mobilization of bacilli" was only a myth, yet it has been almost impossible to eradicate it from the minds of medical men, and many laymen talk of the danger of exciting activity in latent lesions by the use of tuberculin.

Further pathological study has shown that there is a tendency for the tuberculous process in the lung to show an increased destructive activity and a rapid dissemination of infection immediately prior to death, thus causing many miliary tubercles to be found in parts of the lung which had shown few changes during the life of the patient. This occurs whether the patient is treated with tuberculin or not and is an expression of the final exhaustion of the defensive forces of the body. In spite of the fact that this is common knowledge to those who are intimately studying the clinical and pathological changes which occur in fatal tuberculosis, yet it has not been sufficient to supplant the wrong impression that was given out when tuberculin was on its first trial. Neither has the fact, that the many clinicians who are using tuberculin intelligently throughout the civilized world have failed to see latent foci start into activity and failed to see miliary tuberculosis result from the proper administration of tuberculin, been able to remove the "mobilization myth." It seems easier to accept myths than truths. Neither has this cumulative experience been able to wholly remove the unwarranted fear, although it now seems that it is rapidly disappearing before the twenty years of experience in the successful use of the remedy.

When a supposed fact creeps into medical literature it is handed down from generation to generation, by both tradition and textbook, without being questioned, especially if it has emanated from a man of recognized eminence. While conservatism

in medicine is to be desired, yet it makes it necessary for students of medicine to spend a great deal of energy in learning traditions which, when they are able to do independent thinking, they will sooner or later be compelled to learn are untrue. Medical literature contains many general statements, this in spite of the fact that there is little place for general statements in medicine. These, however, in conjunction with the general mental inertia which characterizes human beings as a whole, make it almost impossible to introduce new facts, and equally impossible to rid our literature of error when it has once been accepted; for each new fact or theory is opposed by some general statement which has become a guiding principle. Accurate observation and calm, unimpassioned judgment are the parts of a genius, but unfortunately, the work of a genius is recognized slowly.

Koch, the greatest genius of modern medicine, the master of them all, suffered because he was a genius, because he was a pioneer. The things which he did could only be appreciated years after they were announced. The result was that, instead of being appreciated, he was maligned by the very profession that should have worshiped him. His severest censure came because of his production of tuberculin; and after all the abuse and slander which were heaped upon him, we now know that he was right. Fortunately, he lived long enough to see that the medical profession was going to come finally to an understanding of tuberculin and recognize its value. Fortunately for the world, but unfortunately for himself, he made other discoveries —notably, that human and bovine tubercle bacilli are different— and again he was maligned and mistreated because he had announced another scientific fact for which the world was not ready and which it was unwilling to receive. This fact, however, greatly simplifies the problem of the prevention of tuberculosis, for it shows us where the main source of infection is, and helps us to direct our protective measures more intelligently. It was right that judgment should be withheld and the question be convincingly settled before being accepted; but it was not the part of open-minded scientific men to oppose the man with bitterness because they were unwilling to accept this announcement. If one will study carefully the writings of Koch and see the calm, unimpassioned judgment which pervaded his work and see the strictures he put upon his results before accepting them,

he will learn that when Koch made an announcement it was first substantiated by facts.

Tuberculin, along with many other important scientific discoveries, now stands a monument to his greatness, but only after it had fallen into a disrepute second to no other measure ever introduced to the medical profession.

The fact that tuberculin was saved from the wreck of 1890–91 is largely due to the pupils of Koch. Those who had worked with him and knew the facts as outsiders could not know them all believed implicitly in the master. They were convinced by the good they had seen, while outsiders were alarmed by the harm that had come to their notice.

During the next few years following 1890–91, the use of tuberculin was confined to a small handful of men who were carefully studying the best methods for its administration. In Europe those most closely connected with it were Carl Spengler, Petruschky, Thorner, B. Fränkel, P. Krause, Goetsch, Bandelier, Guttmann, and later, Turban and Moeller. In England, Heron and Wilkinson, and in America, von Ruck, Trudeau, and later, the writer.

Immunizing Power of Tuberculin Shown by Animal Experiment.—It has been brought forth as an argument against tuberculin that it is impossible to immunize healthy animals by injecting them with tuberculin. This cannot be recognized as an argument. It is based on a lack of appreciation of what tuberculin is expected to do. One of the earliest conclusions of Koch was that tuberculin acted differently upon healthy and infected guinea pigs. He showed that when injected into guinea pigs that were infected there was a tendency for the tubercles to heal and the life of the pigs to be prolonged beyond that of the controls. This is positive proof of a relative immunity. This is all that can be produced by any means that we know. Kitasato, Spengler, Denys, and many other observers have reported this same thing.

When guinea pigs are inoculated subcutaneously with virulent tubercle bacilli, in about two weeks' time a tuberculous ulcer appears which remains until the death of the animal, which occurs in from two to three months' time. If the inoculated pigs, on the other hand, are treated with tuberculin, the treatment being begun soon after the inoculation, the animals will live more

than twice as long, and the ulcer at the point of inoculation will often heal. Kitasato in writing on his experiments says: "I was able to convince myself with the greatest certainty that even tuberculosis of the lungs has been influenced in a decidedly favorable way by tuberculin treatment"; and further, "In the case of those guinea pigs, five in number (they are still alive seven months after the infection), the inoculation ulcer is completely healed; the lymphatic glands previously swollen are no longer to be felt; and the animals have steadily increased in weight and have in all respects the appearance of healthy animals." (Quoted by Wilkinson.)

So, while experiments have not succeeded in making it possible to thoroughly immunize animals against inoculation with large numbers of virulent bacilli, yet numerous observers have reported that a certain amount of immunity has been conveyed to guinea pigs by treating them with tuberculin previous to inoculation, and the lives of pigs which were previously inoculated have been markedly prolonged by tuberculin when the remedy has been begun soon after the inoculation has been made as mentioned above. In this connection it must not be held against tuberculin because it will not produce absolute immunity, for we know of no absolute immunity in this disease; and further, it must be remembered that there is probably considerable difference between the immunizing power of living tubercle bacilli and that of tuberculins or dead tubercle bacilli. It is evident that there is something in the living micro-organism that calls forth the more powerful response on the part of the animal organism. We do know that inoculation with small numbers of virulent tubercle bacilli will produce immunity against virulent strains. The degree of immunity to be obtained in this way is still to be determined, but it, too, seems to be only relative. We also know that animals which have been previously infected with tuberculosis, when treated with tuberculin, develop quite a high grade of immunity, a higher grade than that obtained where healthy animals are treated with tuberculin; therefore it seems that an infection from living bacilli changes the cells in such a manner that they respond in the production of specific immune substances differently to the injection of tuberculin from what they do when no infection is present.

Lack of Knowledge of Tuberculin.—The men who used tuber-

culin during this early period of trial knew very little more about tuberculin than that it was made from the culture broth on which tubercle bacilli had grown. Its action was based on principles of immunity which were unknown at the time and which are not wholly understood today. There was no theory of its action except the one suggested by Koch: namely, that its purpose was to produce sufficient stimulation in the focus of infection to increase necrosis and thus separate the healthy from the diseased tissue. The difference in its action in different stages of the disease and according to the different-sized doses, and the theories which satisfy us to a certain extent today as to its method of action were all unknown at that time; consequently men were attempting to use a remedy which they did not know and to treat a disease, the pathology of which they did not understand. Failure was inevitable, but of course they did not know it. This had to be found out by trial; and an unfortunate trial it was.

The saddest thing about tuberculin treatment today is that men are continuing to use it who are not acquainted with the literature, who have never made any study of the remedy, who do not know how it is made, or what it is supposed to do, who have given only a passing thought to tuberculosis, consequently fail to comprehend it either in its clinical manifestations or as a pathological process, and yet they are expecting to get results; at least, they are offering to treat patients who are suffering from tuberculosis with it. That they fail is a foregone conclusion; but the unfortunate patient will only find it out by experience.

The carelessness which attends the employment of tuberculin by some clinicians today is doing a great deal toward retarding its general acceptance. The sins of the administrator are assigned to the administered.

Recently a patient consulted me who had been treated with tuberculin one year previously by his family physician. After examination I suggested the use of tuberculin. He demurred, saying that he could not stand those treatments again. I answered that there was nothing to stand, for there was no pain or unpleasant feelings connected with the treatment. He then said that during his previous course of treatment he had received injections every five days, had kept no temperature chart

or record of other symptoms, and that almost every injection had been followed by chill, fever, and prostration, which made it necessary for him to go to bed for a day or two. The physician told him that it all belonged to the treatment.

Another patient gave the following amusing (if it were not serious) description of the manner in which she was treated by a man who conducts a small sanatorium and professes to be a specialist in diseases of the chest. She said the medical director spent one week in a neighboring city and learned how to give tuberculin. He gave his doses every Tuesday. He never looked at the temperature chart, nor inquired into the accompanying symptoms; the nurse always remembered the last dose.

Such methods cannot do other than discredit the remedy, and they are to be deplored. I hear mutterings on all sides against tuberculin, but always from men who have not taken the pains to learn how to employ it correctly.

In measuring the value of tuberculin it must not be judged by the worst that is done by those who administer it carelessly, but by the best that is produced by those who use it intelligently. It behooves its friends to be on their guard in order to save it from disrepute. While its action in healing tuberculous infection is unquestioned, its results are produced slowly and therefore apt to be overlooked. If the benefit that comes from a prolonged course of tuberculin treatment should be produced as quickly as an appendix is removed by the knife, there would be no question as to its recognition. It will cause tubercles to heal, but, unfortunately, it requires time, not a few minutes, but many months.

Lack of Knowledge Concerning Tuberculosis.—In 1890 and 1891, very little was known regarding tuberculosis as a clinical disease or a pathological entity. The study of this disease was stimulated by the unfortunate trial of tuberculin. Prior to this time it had been considered uninteresting, and its study had been looked upon as fruitless. Today there is no excuse for a man who desires to treat tuberculosis not having the opportunity to study its pathology, neither is there any excuse for his not being able to form a fairly accurate judgment of a case as it presents itself clinically, because the knowledge and opportunity are at hand. Books describing the disease and the principles of its treatment are plentiful, and clinics where tuber-

culosis is being treated intelligently are found on every hand.

It is not sufficient in treating tuberculosis to determine that tuberculosis is present; it is necessary for the clinician to form a definite idea of the pathological picture which is present. He must correlate his physical signs and his pathology. He must be able to determine what conditions are removable and what ones are not removable. Until he does this he will not be able to give an opinion as to whether tuberculin or any other remedy is doing good. Of course, the disappearance of symptoms and the putting on of weight (without stuffing) may be taken as an indication of favorable progress of the patient, but it is of little value in giving an opinion as to whether tuberculin is doing good or harm. The physician, knowing what tuberculin can do, and knowing the pathology of his tuberculous process, should be able to judge fairly accurately as to what can be expected in a given case. Of course this was out of the question in the early nineties. It is almost wholly out of the question today, not because the knowledge is not at hand but because it is not made use of. Comparatively few medical men are giving sufficient attention to tuberculosis to be able to say, "This area of the lung is active," "This is breaking down," "Here cavity formation is occurring," "There fibrosis is taking place." Yet this is essential if one is to give an opinion with any degree of accuracy as to what a given patient's chances of cure are, and if they are to give an intelligent opinion as to the action of this remedy more accurate examinations are indispensable to success.

Tuberculin also suffered because clinicians did not appreciate the clinical course of tuberculosis. Tuberculosis is a disease that does not run an even course. The symptoms are now prominent, now in abeyance. Cough, expectoration, temperature, and the general feelings of the patient go in waves, now better for a short time, now worse for a while; and unless this is appreciated, an opinion cannot be given. This condition obtains whether the patient is treated with tuberculin or not, but in those cases which are treated with tuberculin it is very natural for the clinician to ascribe any increase in symptoms to the tuberculin. Tuberculin may be given absolutely correctly, and yet the clinical symptoms of the patient change for the worse. It requires a good deal of judgment to rightly interpret these changes; but unfortunately, tuberculin has nearly always suf-

fered and been blamed for these changes by those who did not understand their pathology and the clinical course of the disease. To give an opinion on the value of tuberculin, one must: first, understand tuberculin; second, understand the pathology and clinical course of the disease; third, be able to map out with a degree of certainty the changes that are occurring in the lung; and then, use his judgment as to whether these changes are natural or whether they are hastened by the use of the remedy. Tuberculin can do great good, likewise untold harm. In this it is not peculiar. It is like every other remedy. It requires intelligence for its use, and when we consider the seriousness of tuberculosis, it is not too much to ask that our treatment of this disease be governed by extreme caution and our best judgment.

Another unfortunate condition which has worked against the adoption of tuberculin is the fact that the patients under treatment have not been observed sufficiently closely. I know of numbers of physicians who are treating tuberculous patients, who rarely examine a chest after the first examination is made; and some even who have depended entirely on the examination of the sputum to make a diagnosis, and have put the patient on tuberculin without making a physical examination. We know of patients who are being treated without any observation of their temperature, and many who are under treatment without full instructions as to the method of living. All these things cause physicians to make such statements as, "I cannot see that tuberculin does any good." Of course it doesn't do any good. It cannot do any good under such circumstances; but it is not tuberculin that is failing—it is the physician.

Lack of Unanimity of Opinion of Friends.—Probably one of the most confusing circumstances connected with the administration of tuberculin is the lack of unanimity on the part of those who are friendly to its use. Some favor small doses; others favor gradually increasing and large doses; some have a horror of reactions and think them wholly bad; others think them harmless but try to avoid them; and still others think them necessary and accompanied by beneficial results. Some have a definite interval at giving doses; while others believe that individualization is the best method.

The result of all this difference of opinion is a ge

fusion. Those who are not thoroughly convinced of the value of tuberculin produce the argument that, if those who are so thoroughly in favor of it differ so in their methods of using it, it is plausible to suppose that they are wrong in their observations of its value. They take the position that if the friends of tuberculin cannot agree on how it produces its good results and on the best method of its administration it is also likely that they might be mistaken in their observation as to its favorable action. While this argument seems plausible, yet I think these differences in opinion in its administration can be largely harmonized. They are based upon different conceptions that different observers have of the remedy.

The action of tuberculin, as I have shown, is a complex one. It consists of two very distinct processes, both of which are specific: one is the stimulation of the body cells to the production of specific antibodies; the other is the stimulation of the focus of infection. Depending on the physician's idea of what he is trying to do, he may favor one or the other method of administration more, according to what he believes the most important result to obtain. If he thinks the specific antibody formation is the chief aim, and the focal reaction to be avoided, he will follow one line. If he thinks the focal stimulation of equal or more value than the immune response, he will follow another.

I shall risk the confusion that might result by giving the opinion of a few of the men who are particularly interested in tuberculin therapy, that my readers may see their differences, and then I shall try to point out the difference in their point of view and see wherein each is right, and wherein each is using the remedy to the advantage of the patient.

Wright [1] says:

> I obtain almost every day maximal immunizing responses from the inoculation of doses of tuberculin which have not produced any constitutional disturbance. Further, I have for periods extending over a year continued to inoculate with doses of new tuberculin corresponding to from $\frac{1}{1000}$ to $\frac{1}{600}$ milligram of tubercle powder without registering any falling off in the immunizing response. Again, I have in some of these cases repeatedly registered worse and not better results whenever larger doses than these were employed. Lastly, I have before my mind the fact that the horses which are, in connection with the manufacture of diphtheria antitoxin, inoculated with

[1] Studies On Immunization, 1909, page 274.

large doses of diphtheria toxin, all sooner or later lose their power of responding to the stimulus of inoculation, and recover that power of response only after a long period of rest.

In view of these facts I would submit that the whole question of dosage requires to be reconsidered. For myself, I am day by day more impressed with the fact that the machinery of immunization can be brought into action by very small stimuli and that it can very easily be overtaxed. In accordance with these facts I regard it as a matter of great moment, especially in connection with immunization against tubercle, to employ in every case the smallest dose which will elicit a satisfactory response; to repeat the dose only when the effect of the preceding inoculation is passing off; and to increase the dose only when it becomes clear that the dose previously employed is ceasing to evoke a sufficient immunizing response. Acting in accordance with this principle, I now begin with a quantum of tuberculin corresponding to not more than $\frac{1}{1000}$ milligram of the tubercle powder, and now never advance to doses larger than $\frac{1}{600}$ milligram.

Trudeau [2] says:

From my own experience with tuberculin I have formed the impression not only that fever reactions are not necessary to obtain good results, but that, although occasional moderate reactions are unavoidable and apparently do no harm, every effort should be made to avoid them. If frequent and violent they have a bad effect on the patient's general condition, and are by no means free from danger, as was shown during the early history of tuberculin treatment, the danger being the production of continuous fever, cachexia, and increased activity in the disease.

The best method has seemed to me to begin with very minute doses, $\frac{1}{10000}$ or even $\frac{1}{20000}$ of a milligram of solid substance Koch's Bacillen Emulsion, or a $\frac{1}{1000}$ of a milligram of old tuberculin, and increase so gradually and at such intervals as to carry the patient to full doses with as little disturbance as possible; and by taking sufficient time, most patients can be taken through the entire treatment with but occasional and moderate reactions. At the slightest evidence of intolerance, as manifested, not only by the patient's temperature, but by his symptoms, by marked irritation at the site of injection, or depreciation of his general condition, the interval between the injections should be lengthened and the dose diminished for a time. Care should be taken never to inject after a reaction until all effects of the previous reaction, both on the patient's temperature and general condition, have entirely passed away. I have also formed the impression that the treatment should be extended over as long a time as is needed to avoid reactions, no matter how long that may be, and that time is an important element in obtaining the best results. Six months of treatment is almost always necessary, and a year or more would be better in many cases.

[2] Report of the Second Annual Meeting of the National Association for the Study and Prevention of Tuberculosis, Washington, pp, 303–5.

Bandelier and Roepke [3] say:

The maxim to remain as close as possible to the reaction limit without well-marked or severe reactions occurring coincides with the experience that the most evident results have been obtained with slight reactions up to 38°, or a little over. . . . The beginner should lay special stress on the avoidance of reaction. Its attainment will also depend on the individual susceptibility to tuberculin, on the severity of the disease, and on the general constitution. . . . It is only in the rarest cases possible to fulfill the demand to avoid febrile reaction altogether. Observing all precautions, fever will sometimes occur after an injection. A pause of several days should then be made after the temperature has fallen, and the same dose then repeated. As a rule, this repetition causes no further rise of temperature, or at any rate, only a slight one; in the latter case the same dose should be repeated, if necessary even a third time.

It need only be said here that the original method of giving doses daily, which still has some vogue, is inconsistent with the mild, reactionless method, since even febrile reactions may not make themselves felt for twenty-six to thirty hours. . . . If the basis of the modern view is accepted, that one aspect of the action of tuberculin rests on the systematically acquired tolerance, a gradually acquired immunity to the toxins, then the employment of larger doses of tuberculin cannot be dispensed with.

Sahli [4] says:

The production of local inflammatory reactions by tuberculin is risky and uncertain, and I am convinced that it is far wiser to avoid, as far as possible, all such local reactions by careful regulation of the tuberculin dose.

With regard to frequency of injection I recommend that these should be given not more often than twice a week; in the case of the stronger solution (perhaps from C. onward, referring to Béraneck's tuberculin) only once a week, and after the maximum dose is reached as seldom as once a fortnight.

Pottenger [5] says:

The dosage of tuberculin is modified by many influences, such as individual susceptibility, the character and location of the lesion, whether it is extensive or circumscribed, active or quiescent, according to the conditions under which the patient is being treated, whether in an institution or in ambulatory practice; whether he is resting or working; according to the accompanying complications and conditions, such as colds, influenza, bronchitis, hemorrhage, menstruation; also according to the preparation employed. There can be no set rule. The man who understands this remedy individualizes and aims at the production of results. He forgets stated intervals, and rules for in-

[3] Tuberculin Diagnosis and Treatment, American edition, William Wood & Company, 1909, p. 95.
[4] Tuberculin Treatment, 1912, pp. 21 and 52.
[5] Some Difficulties Encountered in the Therapeutic Use of Tuberculin, *Journal of the American Medical Association*, Sept. 16, 1911.

crease of dosage, and is guided entirely by the effect obtained. A hypodermic syringe filled with tuberculin cannot cure tuberculosis.

Wright is a champion of small doses given at infrequent intervals and not increased unless the increase is necessary to produce an immunizing response. His advocacy of the small dose comes from the fact that he has studied the cure of tuberculosis in connection with his observation of the opsonic power of the blood, and has taken this as his guide to dosage. The purpose of Wright's method is the increasing of the opsonins of the blood. He has found that small doses of tuberculin will do this, and as he has found healing to take place coincident with these changes in the blood, he has established this as his method of treatment. In this connection I would call attention to the fact that Wright's treatment has been largely confined to localized tuberculosis. His experience has not been large in the treatment of widespread lesions, especially advanced pulmonary tuberculosis. The phenomena following Wright's method of dosage are schematically shown in Fig. 29, 1, page 179, where they are contrasted with those following the production of toximmunity.

A peculiar feature of Wright's work is his respect for the negative phase. He has found that following an injection of tuberculin there ensue certain definite phenomena. Soon after the dose is administered there is a drop in the opsonic power of the blood. If the dose is correct in size and administered at the proper time after a temporary drop, there is a rise in the opsonic content of the blood. He has also found that it is advisable to keep the opsonic content as high as possible; therefore he has learned to have great respect for the negative phase and not repeat an injection during this phase, for by so doing he has found that the negative phase may be exaggerated, producing what he believes a condition when the patient is in great danger. I shall discuss the negative phase elsewhere in more detail. Wright's method consists in producing independent individual responses, by giving each dose on the "c" portion of the curve (Fig. 28, page 177).

It will be seen that Wright's work does not properly take into consideration other factors in cure. He does not consider that there are other antibodies than opsonins. He seems to leave them out of account in his estimation of the patient's immunity.

He pays little attention to focal stimulation. We must recognize that even small doses of tuberculin probably produce a certain amount of stimulation at the focus of infection; but from my study of localized tuberculosis as it can be observed in the larynx or pharynx, or wherever tuberculous processes are visible, I have noticed that small doses do not produce much visible focal stimulation, and that, if the focal stimulation is to be kept up, it is necessary to gradually increase the amount of tuberculin given. From my discussion of why artificially administered tuberculin aids in cure where spontaneous cure fails, it will be remembered that I lay special stress on the fact that the focal irritation controlled by the proper administration of the remedy is probably a big factor in healing.

As mentioned in my former discussion, the patient never dies from the original focus, but only after the disease has extended. The extension of the disease is prevented by keeping up a satisfactory immune content of the blood, so that when bacilli escape from the foci of infection they are seized upon and destroyed by the immune bodies. Now, either small doses or large doses will stimulate the physiological processes of the body to the production of antibodies, and either one in this way will help to bring about cure, by preventing new infections occurring while the healing of the original focus is carried on; and in this connection I should like to repeat what I have mentioned previously, that the small dose probably does produce certain changes in the focus of infection which are favorable to healing, but it fails to produce the more marked stimulation which often seems to be necessary to bring about cure. It also seems that the general testimony of observers is to the effect that larger doses of tuberculin are followed by the greatest number of antibodies in the blood.

By those who consider it necessary to gradually increase the dose and eventually produce quite a toximmunity to tuberculin, both factors in the production of immunity are considered; for it must be remembered that either small or large doses, unless they be so large that they overcome the patient's power to produce immunizing substances, have the effect of increasing the immune content of the body, although not always to an equal degree. The focal stimulation is far more marked when large doses are employed; that following small doses is slight and at

times clinically imperceptible. (The production of toximmunity is schematically illustrated in Fig. 29, page 179).

From this explanation we can see that good results may be produced by either large or small doses, but that the two are suited to different conditions. We may infer, and in this clinicians of great experience agree, that the gradual increase of dosage seems to give us a better method of applying the remedy because its action is in accord with the complex requirements necessary to produce healing. It fortifies the body against the escape of tubercle bacilli from the focus of infection, and at the same time, it produces the necessary condition in the blood which causes the focal stimulation necessary for healing.

Schröder is particularly careful not to destroy the patient's hypersensitiveness. He thinks doses should be used which will maintain this, and utilize it to the greatest extent. His method consists of slow increase and infrequent dosage.[6]

Whether reactions are beneficial or harmful depends entirely on conditions; but whether we think they are harmful depends on our ideas of how they are produced. This is one of the subjects on which we cannot make a general statement, except to say that all reactions are not harmful, neither are they all beneficial.

A temperature reaction is a manifestation on the part of the organism of its ability to cope with some pathological process. We formerly looked upon fever as a bad symptom and endeavored to reduce it by all methods possible, such as cold baths and antipyretic remedies; but we have recently learned to consider it as an index of the ability of the organism to react. We now know that the danger time in infection is not when the fever is high but when it is low, because the failure to respond shows that the body cells are no longer able to carry on their fight against toxins, to respond with the production of increased temperature. I look upon the fever reaction following a dose of tuberculin the same as the fever reaction following the administration of any other bacterial vaccine. Therefore, it is not the rise in temperature which is harmful, but the condition which produces it and which at the same time causes the phenomena which often accompany it, and which are carelessly attributed to it.

[6] *Brauer's Beiträge zur Tuberkulose*, Bd. XXIII, p. 21, 1912.

The tuberculin temperature reaction, according to our theory, shows that the toxins which have been introduced into the body are being cared for, but that they are in excess of the amount that can be satisfied by the free-circulating receptors. If they reach the focus of infection they also produce a focal reaction.

While we are apt to consider that the fever reaction is an index of the character of the focal reaction, this is not necessarily true. It is possible to have a marked focal reaction without a temperature reaction, and we know from our experience in observing local tuberculous foci that it is possible to have a fever reaction without a marked focal reaction; nevertheless, in the administration of tuberculin, we must give considerable attention to the effect of a given dose of tuberculin upon the temperature curve. This, however, should not be done to the exclusion of our observation of other phenomena, such as the clinical symptoms of malaise, aching, nervousness, the local congestion where the focus is visible, signs of increased irritation in areas in the lung as shown by increased cough and expectoration, a feeling of constriction in the chest, and increase of physical signs upon physical examination.

In the treatment of tuberculosis it is extremely desirable to have a focal reaction, but it is likewise necessary to have these reactions under control. The severity of the focal reaction which can be permitted without producing harm depends very largely upon the character of the process that we are treating. If we have a small circumscribed lesion, a marked focal reaction produces no harm, and little fear need be had even if several focal reactions should occur during the process of treatment. If, however, the process is decidedly active and more extensive, then a marked focal reaction might be harmful, although, as a rule, even here a single one would not prove to be so. Only repeated focal reactions are to be feared.

It must be the experience of many who have used the subcutaneous test to any great extent that, occasionally following the general reaction which occurs with the diagnostic dose of tuberculin there is a marked improvement on the part of the patient thereafter. This is not a result of a great increase in antibodies in the blood, neither is it the result of the fever reaction, but it is a result of the specific reaction which occurs in the focus of infection, which stimulates the process to repair.

The significance of the focal reaction should be well understood by all those who are treating tuberculosis, for in the therapeutic use of tuberculin it should be our purpose to control carefully this reaction.

Wright has suggested as an explanation of the harmful results in the early trial of tuberculin that they were due to the repeated injections of large doses of tuberculin, keeping the patient constantly in the negative phase, thus destroying his power to react with an immunizing response. This enabled the disease to spread, and as a result, destroyed the patient.

This, however, does not seem to me to be the full explanation. While we must recognize the fact that the power of producing antibodies in all probability is lowered by such large doses as were administered at that time, yet, according to the post-mortem findings, it is evident to me that an equally important factor was the severe focal stimulation that was produced by the large doses given and which was repeated by the next injection, often given before the effects of the previous one had disappeared. This stimulation was so great that, instead of favoring healing, it forced the destruction of tissue, thus causing severe inflammation in the foci of infection and the rapid disintegration of tissue, together with the liberation of toxic material which resulted in the death of the patient. This is especially evident because of the stage of the disease that was being treated, many patients being treated who had widespread lesions and who were within a few weeks of death.

Friends of tuberculin also differ materially in their opinion as to the spacing of doses. It cannot be denied that tuberculin is capable of producing beneficial effects when given in various ways; in fact, the patient in treating himself from his own focus does not give it with any degree of regularity, but we are trying to produce a result when nature has failed and, unless we can do more than she has already done, we shall also fail. In such case we come to the rescue by natural methods from without. It is necessary for us to take advantage of the knowledge that we have of both her successful measures and her shortcomings, for we are forced to take the cases which she fails to heal spontaneously and endeavor to heal them artificially; and since she has failed, it would seem best to adopt measures somewhat different from the ones which she has been employing.

There are excellent authorities and able clinicians who are endeavoring to devise a set way of giving tuberculin so that it can be given by rule. We cannot deny that these men have obtained excellent results by so doing. On the other hand, there are others, among whom is the writer, who endeavor to recognize that the keynote in the proper administration of tuberculin is individualization, suiting the remedy, both in size of dose and space between doses, to the patient and the special peculiarities of his tuberculous process. I cannot believe that the best results can ever be produced in any remedy by routine administration. Routine can be followed so far, but the successful therapist is the one who breaks routine at the right point and adapts the remedy to the conditions which he is treating.

CHAPTER IX.

EVIDENCES OF THE THERAPEUTIC VALUE OF TUBERCULIN.

If we sum up the evidences which have been adduced during the twenty years' use of tuberculin, we find that there is a great deal of positive evidence that can be introduced to its credit.

Tuberculin Increases the Percentage of Cures.—A favorable result is obtained in a greater percentage of those treated with tuberculin than those treated without tuberculin. This observation is now so general that it needs no statistics to support it. Even those who are not enthusiastic about tuberculin mention that it seems to be of value in those cases which are at a standstill, or not progressing favorably with the hygienic-dietetic treatment alone. If they only recognized it, this is one of the best evidences that can be adduced in its favor. If it will start those patients on the road to recovery, who are not doing well, would this not also argue that it would be of value in the earlier and more favorable cases? Would it not be logical to suppose that it would also hasten their recovery if it were used? Any remedy which is of value in less favorable cases should be of value in more favorable cases. If tuberculin will start those patients toward cure, who are not progressing as they should without its use, there must be something in its action which is of value in all cases of tuberculosis, because these are the ones which, under ordinary circumstances, will not go on to cure.

If tuberculin is given properly, nothing but good can come from its administration. It will be recalled that I mentioned that tuberculosis always heals by inflammation, that there is a certain amount of focal stimulation necessary to cure. This focal stimulation is a very complex phenomenon. It is a specific inflammation—that is, an inflammation which is caused by the specific products of the tubercle bacillus administered either naturally by autoinoculation or artificially; and inasmuch as tuberculin, when administered artificially, will produce this focal

stimulation, it is of value in treatment. In the healing of tuberculous lesions, focal stimulation is important; the focal reaction is probably dependent upon the specific reaction which takes place when the toxins and antibodies combine in the tubercle.

The advantage of the artificial method of administering tuberculin must not be overlooked. In the natural cure of tuberculosis, as mentioned elsewhere, the probabilities are that small quantities of toxins are more or less constantly thrown out into the blood-stream. Resulting from this, there is a more or less constant stimulation of the machinery of immunization; yet, this stimulation is rarely marked; for, unless the quantity of toxins be large, which, under ordinary circumstances, is not true, it would be slight or negligible. The focal stimulation in the natural cure is also, as a rule, negligible, and just to that extent fails to produce healing. When tuberculin is used artificially, on the other hand, we give a dose, then after a certain time, another one still larger, and continue, increasing the amount, always producing a definite focal stimulation. The dose of tuberculin is increased sufficiently often when it is properly administered to insure the occurrence of a focal reaction every now and then. This is probably one reason why the artificial administration produces cure when the natural process has failed.

Inasmuch as the tuberculin furnished by autoinoculation escapes from the tubercle and is applied at once, it is probable that smaller quantities of toxin will produce focal reaction when administered in this manner than when given artificially.

Many clinicians begin the use of tuberculin as an experiment with their minds prejudiced against it, believing that it is unnecessary as a therapeutic agent and that they could produce as good results without it as with it, but after a definite trial, become thoroughly converted to its use. It is a notable fact that no great clinician has learned to use tuberculin correctly and given it up as a therapeutic measure.

Not only do we see the value of tuberculin in early cases, but it is probably in advanced cases where it is relatively of the greatest value to the patient. Slight tuberculous lesions will heal in a very large per cent of cases without tuberculin. It is probable that tuberculin will add not less than 20 or 25 per cent to the chances of cure, but this is not all the good that it will do. It will bring about cure in a much shorter time. The necessary

period of treatment where tuberculin is intelligently used is much shorter than where hygienic measures are depended upon alone.

The pathological process in advanced tuberculosis is by no means simple. On the contrary, it is extremely complex. The chance of spontaneous cure is very slight; and the condition is so serious that everything which will help must be used. In advanced cases hygienic measures will do a great deal. They will increase the patient's resisting power, improve the body nutrition, stimulate the functional activity of the cells, and in this way strengthen the organism so that when the bacillary products are thrown out from the focus of infection the machinery of immunization will be ready for response and will produce the greatest amount of antibodies possible from the given stimulation. In this way some cases even of advanced tuberculosis will eventually heal; but the difficulty with this program is that it is relying upon a slight stimulation when probably a larger stimulation is necessary. The cells are ready to respond, but the specific stimulation is lacking.

When tuberculin is added therapeutically the necessary stimulation is provided, and this results in greater focal stimulation and more rapid healing. Contrary to the preconceived ideas of most clinicians, advanced tuberculosis profits relatively more by the artificial administration of tuberculin than does early tuberculosis. In this connection it should also be mentioned that there is a greater tendency for the disease to spread in advanced tuberculosis, and this is counteracted by the high immune content of the blood, produced by the artificial injection of the remedy.

While it seems almost useless to give statistics to demonstrate the value of tuberculin in therapy, yet I will add the comparison made by Moeller,[1] who chose one hundred cases treated by him in ambulatory practice with tuberculin and compared the results with one hundred treated without tuberculin. The results were as follows:

		NO. PATIENTS	CURED	
I	Stage without tuberculin	32	8	28.1%
I	" with "	42	25	59.5%
II	Stage without tuberculin	34	0	0 %
II	" with "	38	11	28.9%
III	Stage without tuberculin	34	0	0 %
III	" with "	20	0	0 %

[1] Lehrbuch der Lungentuberkulose, Wiesbaden, 1910.

These statistics are similar to those of other observers. I am of the opinion that tuberculin when given correctly and added to the usual hygienic-tonic treatment of tuberculosis adds anywhere from 20 to 25 per cent in early cases to practically all the chances the patient has in some of the advanced ones, such as those accompanied by tuberculosis of the larynx.

Statistics are very indefinite things. They depend a great deal upon the individual observer. Oftentimes men are misjudged by the statistics which they publish. A young man with slight experience may produce better statistics than he will when he has had more experience, for he sees things later with a better trained judgment. He may have been just as earnest and just as honest in his early work; yet he may not have been able to judge the case or result as well. An optimist will always get better results than a pessimist, partly because he counts results that a pessimist is afraid to count and partly because he inspires his patients and carries them along to a more successful result.

Tuberculin Prevents the Spread of Infection.—I have frequently made the statement that no tuberculous patient has ever died of his original infection. This is true in one sense and probably in another sense untrue. My meaning is that the original infection, which is usually small in size, does not destroy the patient. The patient does not die from tuberculosis so long as the disease can be kept to the small primary focus; but the cause of death is usually due to the disease spreading from this focus and gradually encroaching upon larger and larger areas. Why a lesion will remain latent for many years and then become active is not known. Whether it is due to a primary activity on the part of the bacilli, by which they multiply rapidly, or whether it is primarily due to certain changes in the tissues, themselves, which permit the bacilli to become active, we do not know; but whichever it is, it seems that after a prolonged period of latency conditions often become right for the infection to spread. This emphasizes the importance of healing these early lesions, if it is possible to do so. If it were possible to bring the early infections under treatment at a time when the lesions are so small that the bacilli would all be destroyed, this would be ideal; but while this may not be practicable on account of our shortcomings in diagnosis, it is practicable to heal them out while the

lesions are comparatively small, and thus reduce to a minimum the danger of developing activity later.

Often, after these old foci have been quiescent for a considerable time, the specific bacillary products which keep up the stimulation necessary to the formation of antibodies cease to escape, and accordingly the immune content of the blood becomes gradually reduced; therefore, when, for some unaccountable reason, the bacilli in these old foci become active, the conditions present are favorable for a rapid spread of the disease. The number of bacilli escaping from these old foci is often quite large, and taking advantage of the low immune content of the blood, they readily produce infection. The safety of the patient with a tuberculous lesion then depends upon the high immune content of the tissues, because he must every now and then be subjected to the danger of an attempt on the part of the bacilli to escape and start up new areas of infection. When the disease is active the danger from the scattering of the bacilli is much greater than when quiescent. It has been definitely shown that tuberculin injected artificially will increase the immune content of the blood; therefore we cannot help drawing the inference that theoretically tuberculin prevents the disease from spreading. Clinically we also find this to be true. We find that the tuberculous process progresses less rapidly under tuberculin treatment than where it is not employed. This is due to the fact that the disease is influenced, not only in its progress about the foci of infection, but also in its tendency to spread.

Fewer Complications.—The patients who are properly treated with tuberculin do not suffer from so many complications as those who are not treated. It is also observed that those patients who are put under hygienic treatment do not have so many complications as those who live in unfavorable surroundings; but when the patient is treated with both tuberculin and the hygienic-dietetic régime, as all should be, the greatest reduction in the number of complications occurs. Tuberculosis of the larynx and of the intestine, tuberculous pleurisy, as well as the more uncommon complications, are comparatively rare in patients treated by tuberculin. When I speak of tuberculin therapy I wish it distinctly understood that I imply not only the use of tuberculin, but all recognized hygienic-dietetic measures as well, for they are an essential part of an intelligent tuberculin therapy.

Tuberculin Shortens the Term of Treatment.—Another advantage in favor of tuberculin is that it shortens the necessary time of treatment. It has a tendency to prevent the spread of the disease and prevent complications in other organs. It heals the outlying areas of infection, and it stimulates all foci of the disease to healing. Consequently, when added to our other measures, it shortens the necessary time of treatment.

Tuberculous Complications Heal More Readily.—Not only do we have fewer complications when the patient is under tuberculin treatment, but when these complications are present they yield more readily than they do under the ordinary hygienic-dietetic régime alone. I shall now discuss some of the more common non-pulmonary tuberculous infections. While they do not always occur as complications of tuberculosis of the lungs, yet they have been so almost invariably in my practice. The same therapy, however, would apply whether they were accompanied by a pulmonary lesion or whether they were independent of such. I look upon these infections, however, as always secondary. I do not believe that tuberculosis of the larynx, intestines, kidneys, bones, joints, or, for that matter, of any of the ordinary extra-pulmonary localizations are primary, except that of the lymphatic glands. This is primary. The rest are secondary, as a rule, to a primary, lymphatic or pulmonary involvement.

Pleural Effusion.—I have found it necessary to aspirate less than half a dozen cases of acute pleural effusion in the last ten years. Patients with a recent effusion, who have been put upon treatment, have usually lost it quickly after tuberculin was begun. I have always thought that probably the stimulation of the foci in the pleura favored the absorption of the fluid.

Tuberculosis of the Larynx.—Tuberculosis of the larynx yields very readily to tuberculin treatment. Since I have been using tuberculin I have learned to look upon tuberculosis of the larynx with less concern than I formerly did. It was formerly thought that "consumption of the throat" was wholly incurable. Of course, what was considered tuberculosis of the throat at that time was only the advanced lesion. Nobody ever thought of diagnosing tuberculosis of the larynx until severe infiltration and usually ulceration were present; but now, that we have learned to recognize early infiltration in the larynx, the same as we do early infiltrations of the lungs and other organs of the

body, we have been able to make a very different prognosis in this affection. I consider the prognosis in tuberculosis of the larynx, when the patient is properly treated with tuberculin, to be about the same as the prognosis in the patient aside from the throat lesion. If it is an early case with only slight infiltration and the pulmonary involvement is small, or if it is more extensive but comparatively inactive, then I look upon the prognosis as good. If there is a slight lesion, or a more extensive quiescent lesion or an inactive lesion in the lung, I even look upon a severe infiltration, or even an ulceration, as having a fairly good prognosis. On the other hand, the prognosis in the case of a slight infiltration in a patient with advanced active tuberculosis is not good; and severe infiltration or ulceration in such a case usually offers a bad prognosis. I do not consider, however, that from the throat lesions alone we should give a hopeless prognosis; but all conditions must be taken into consideration. Our opinion must be based upon a careful consideration of the details relating to the case. When the larynx is involved the reaction in the larynx should be taken as the guide to dosage, the aim being to produce a slight focal reaction and increase the dose only rapidly enough to maintain it.

Tuberculosis of the Intestine.—Tuberculosis of the intestine is always serious. I have seen a few cases which presented symptoms indicative of a slight lesion which seemed to clear up, but of course I cannot be positive whether or not my diagnosis was correct; but when we realize the great frequency of this complication in advanced tuberculosis and then see how few of our properly treated cases develop lesions of this kind, we can believe that it is not improbable that some of these cases heal. The same thing is true without tuberculin treatment. We know that pathologists show us healed ulcers in the intestines occasionally where they have not been suspected during life; and I have no doubt whatever that this same thing occurs in tuberculin-treated cases, and we would expect it to be more common because of the fact that we know that lesions elsewhere heal more commonly with tuberculin than without.

Tuberculosis of the Lymphatic Glands.—Tuberculosis of the lymphatic glands is a very common affection; in fact, the most careful statistics show that tuberculosis is primarily a lymphatic disease. The bacilli may pass through the mucous membranes

of any portion of the respiratory or alimentary tract. If they resist the attacks made upon them by the antibodies in the blood, they are carried, for the most part, to the lymphatic glands. The frequency with which the various lymphatic glands are infected in tuberculosis is now becoming realized. The tracheal and peribronchial glands in children are infected very early. The mesenteric glands are often enlarged, and it is not an uncommon thing to find the cervical glands showing the infection. The infection is most common, however, in the tracheal and peribronchial glands, and unfortunately, in this position it is very difficult to diagnose. Therefore, it remains here unrecognized and unsuspected in a great percentage of cases.

We rarely speak of treating tuberculosis of the glands, however, unless we mean the visible glands, particularly the cervical. This is partly due to the fact that we have not yet learned to diagnose infected mediastinal glands with sufficient accuracy. It is my habit, however, after making a diagnosis of tuberculosis of the glands, no matter where the glands are located, to put the patient immediately on tuberculin treatment. Tuberculosis of the glands should not be subjected to surgery. It is not a surgical disease. Surgery can remove the glands which are visible, but it does not eradicate tuberculosis; for we must consider that there are other glands that are overlooked during the operation or other groups of glands beyond those which are removed, which, although not markedly enlarged, are still most probably infected. I have had but one patient with tuberculous glands operated on within the last ten years, and this was a case which came to me with the glands already suppurating and accompanied by high fever. Tuberculin treatment of visible glands, although slow, is the most satisfactory that we have, and when properly applied will nearly always produce a favorable result.

Genitourinary Tuberculosis.—Tuberculosis of the kidney is primarily a medical disease. I recognize that surgeons will not agree with this statement, for it is their habit and teaching to operate on a kidney as soon as the diagnosis of tuberculosis is made. My reason for opposing this is a simple, but I believe a rational, one. Early lesions in the kidney will often heal under tuberculin treatment, and if they do, we have saved the patient a very important organ. I do not believe that it is advisable to keep up tuberculin treatment too long if the lesion does not heal.

If a kidney was suppurating and the disease was extending or if it was producing fever and other marked symptoms, then it would be folly to try tuberculin for any length of time. Where a lesion is small, however, and the symptoms are not serious, I would urge that every such patient be subjected to a trial treatment by tuberculin before operative procedures be undertaken. If there is any amelioration of the symptoms, I should continue the tuberculin. It is a comparatively easy thing for a surgeon with his highly developed technic to remove a kidney, but this proves to be very serious if anything happens to the other kidney. I have treated several cases of tuberculosis of the kidney successfully. What I mean by successfully is that the kidney lesions quieted down and the symptoms disappeared. I have also had several patients come under my observation who had one kidney removed, only to find out later that the other was also involved. This is a most unfortunate circumstance and a condition in which we would give a great deal to have the other kidney back, even although it might not be perfect. I believe that it is the part of conservatism to remove the kidney at times for tuberculosis, but not until tuberculin has been tried, if the case is at all suited to its use. It must be said in favor of the operation for the removal of the tuberculous kidney that, where the bladder is severely involved, the removal of the kidney often has a beneficial effect in curing the ulceration of the bladder. But the same may be said for tuberculin. In one of the cases to which I referred in which both kidneys and the bladder were involved, the bladder symptoms all disappeared under tuberculin treatment. I know it requires patience on the part of both the patient and physician to carry on the prolonged treatment necessary in these kidney complications, but where a life is at stake, we cannot afford to hasten at the expense of the best result.

Tuberculosis of the Ear.—I have had some very interesting experiences in cases of tuberculosis of the ear. In several instances where patients have been more or less deaf for several years prior to the development of pulmonary tuberculosis, hearing began to improve coincident with tuberculin treatment. In one case, particularly, the patient had been quite deaf, and one day he came to me with great rejoicing, saying that he could hear his watch tick. The hearing in this ear went on to quite a degree of improvement.

Tuberculosis of the Eye.—Tuberculosis of the eye is not a very common complication, and yet it is one that I have had in my practice in a few instances. One patient had suffered from a severe uveitis. After careful tuberculin treatment, this eventually healed. I have also seen cases of phlyctenular keratitis heal under tuberculin. These conditions are considered by Wolff-Eisner as being a sort of abortive infection. They do not seem to take a rapid course, and yet they heal very slowly.

Eczema.—It seems strange to many of us that eczema would have anything to do with tuberculosis; yet there are certain forms of this disease which seem to be associated with the tuberculous infection. Spengler, of Davos, called attention to this several years ago, and Sahli, in his recent work on tuberculin, mentions that he has seen cases of eczema in which tuberculin produced remarkable results. I, personally, have had no experience, but mention this as being of great interest.

Tuberculin Prevents Relapses.—Further proof of the value of tuberculin is found in the fact that of those treated with tuberculin there are fewer relapses than in those who are not treated with tuberculin. This observation is now so common that it does not need statistical support, although the report of Brown and Pope[2] goes into this matter statistically and shows that those patients who had been treated with tuberculin in the Adirondack Cottage Sanitarium showed less tendency to relapses than those treated without tuberculin. When we consider that their report was based upon patients treated years ago, we cannot help but believe that improved methods of therapy will make the percentage in favor of the tuberculin treated much more today than it was then. Any remedy which will stimulate to greater healing and any remedy which will increase the immunizing power of the host must have a favorable influence in preventing relapses. Both of these, tuberculin does.

Experimental Proof of the Value of Tuberculin.—Aside from the clinical proof that I have just mentioned, we have certain experimental proof of the value of tuberculin. Animals which have previously been treated with tuberculin show greater resistance to after-inoculation than those which have not been so treated. This has been shown by the experiments of Koch,[3]

[2] Post discharge mortality in patients of the Adirondack Cottage Sanitarium, *Zeitschrift für Tuberkulose*, Band VIII, p. 533.
[3] *Deutsche medizinische Wochenschrift*, No. 46a, 1890, No. 3, 1891.

C. Spengler,[4] Denys,[5] Courmont,[6] Kitasato, and many others. It has long been known that it is very difficult, if not entirely impossible, to wholly immunize a healthy animal against virulent cultures of tubercle bacilli by tuberculin; yet it is definitely established that tuberculin will produce a relative immunity. Absolute immunity in tuberculosis is unknown, but it seems that in order to produce a relatively high immunity it is necessary to have living bacilli. It is also evident that animals which are already suffering from tuberculosis are capable of developing a higher grade of immunity under tuberculin therapy than are those which have not been previously infected.

The fact that animals, which are treated with tuberculin, develop a hypersensitiveness to living bacilli indicates that tuberculin does produce a degree of immunity, because hypersensitiveness is evidence of immunity.

We must also recognize that there are certain antibodies in the blood which will give us evidence for or against the specificity of a remedy. Wassermann has shown that antituberculin is found in the serum of patients who have tuberculosis and that it is increased with tuberculin treatment. He has also shown that large doses of tuberculin seem to produce more antibodies than small doses. Wright has shown that there is an increase of opsonins in the blood, while Koch, Carl Spengler, von Ruck, and many others have shown an increase in the agglutinins and precipitins.

Pickert and Lowenstein[7] published a very valuable observation showing that, while the serum of normal individuals does not contain substances that will neutralize tuberculin, that of tuberculous individuals, especially those who have obtained an immunity to the higher doses of tuberculin, does. This is shown by the fact that the serum of these patients when mixed with tuberculin is able to weaken or prevent it from producing a cutaneous reaction. It is also important to note that the serum of those patients that offered a favorable prognosis seemed to develop this property earlier and to a greater degree than that of those in whom the prognosis was less favorable. The presence of this antibody is direct proof of a specific protection against tubercle protein, and the fact that it can be increased in amount

[4] *Zeitschrift für Hygiene*, Heft 2, 1898.
[5] Le Bouillon filtré du bacilli de la Tuberculose, Louvain, 1905.
[6] Etude sur les substances solubles predisposantes a l'action pathologie de leur microbes producteurs, *Rev. de Med.*, 1891.
[7] Eine neue Methode zur Prüfung der Tuberkulinimmunität, *Deutsche medizinische Wochenschrift*, 1908, No. 52.

by the artificial administration of tuberculin is positive proof of the specific action of the remedy.

C. Spengler [8] published the observation that the blood-serum is not the chief carrier of immune bodies but that this property belongs to the blood-cells. He also produced a remedy (IK), which is supposed to contain these immune bodies derived from the cells, for the treatment of tuberculosis. His ideas have been largely ignored by laboratory investigators, although many clinicians report having seen definite results from the use of this remedy. Meyer and Schmitz [9] have brought out some very interesting observations, which also show that the red blood-cells are carriers of specific immune bodies in tuberculosis. Tuberculin plus serum of a tuberculous animal and tuberculin plus erythrocytes of a tuberculous animal were injected into other animals with the result that a severe toxemia follows the latter, which is explained as being due to the fact that " the tuberculin comes in contact with a specific reactive substance in the blood, especially in the red blood-corpuscles of tuberculous animals with which it unites, producing toxic substances." The authors further say: "We are further able to show that the blood of healthy individuals does not contain any substances similar to this; so we are now able to fill in some of the gaps that have hitherto existed in explaining the phenomena of the action of tuberculin."

This observation is in harmony with the theory that tuberculin is acted upon in a complex manner when it enters the body, as suggested by Wolff-Eisner. This body, described by Meyer and Schmitz, acts like a lysin, and the toxemia resulting is probably due to the highly toxic substances that are set free by the tuberculin when it is lysinized. It also confirms Spengler's observation that the erythrocytes are carriers of antibodies.

Arneth, after making a careful study of the blood during tuberculin therapy, shows that a very important and favorable change takes place in the leucocytes during tuberculin therapy. It has also been shown that tuberculin produces a positive chemotaxis.

When we carefully consider the testimony given by both clinical observation and laboratory technic, we have ample justification for the belief that the theory of the action of tuberculin is justified by the practical results.

[8] Tuberkulose-Immuniblut, Tuberkulose-Immunität und Tuberkulose-Immunblut (IK) Behandlung; *Deutsche medizinische Wochenschrift*, 1908, No. 38.

[9] Ueber das Wesen der Tuberkulinreaktion; *Deutsche medizinische Wochenschrift*, 1912, No. 42.

CHAPTER X.

FEVER IN ITS RELATIONSHIP TO TUBERCULOSIS.

Few subjects connected with the study of tuberculosis are more difficult to discuss clearly than that of fever. The reason for this in the first place is that the subject of fever in general is poorly understood, and in the second place, the tuberculous process is an extremely complex one; therefore we are attempting to explain a symptom which is not satisfactorily understood as it is found in pathological conditions aside from tuberculosis; and we are trying to discuss it in its relation to certain conditions in tuberculosis, which, in themselves, we do not understand.

Cause of Fever.—We formerly looked upon fever as being something wholly bad, and we considered its action entirely harmful. Today our attitude is different. While there are certain harmful results which accompany temperature, there is considerable question in my mind whether these are due to temperature *per se*. It seems to me, at least equally, if not more, probable, that the harmful results may be caused in part by the same agencies which produce fever. Of course, everyone recognizes the fact that there are certain degenerative changes which take place during a prolonged fever, but I am not sure that the correct cause is commonly assigned to them. It seems to me equally probable that both the increased temperature and the degeneration might have a common etiology.

Some authorities are of the opinion that when the temperature of the body tissues on which the bacilli are growing rises it makes the conditions for the growth of the micro-organisms less favorable. Some writers have observed an increase of antibody production during the fever period. Others believe that it is decreased. However this may be, I would caution lest we place too much emphasis upon the fever itself. Fever is simply a symptom. It is a tangible result but not a primary cause.

Fever may be described as a disturbance in the relationship between heat production and heat dissipation. Anything which

causes a production of heat greater than normal must be accompanied by a greater dissipation if equilibrium is to be maintained. Otherwise a rise of temperature will ensue. Any condition, then, which produces a disparity between heat production and heat dissipation will result in a change of the temperature curve, with either a rise or fall of temperature.

In tuberculosis we are accustomed to speak of a disturbance on the part of the heat center. This is rather a vague expression. We mean to imply by this, however, that the balance between heat production and heat dissipation is so disturbed that upon the least provocation a rise of temperature results. I shall discuss the particular variations in the fever curve more carefully as we study the action of tuberculin; so I will dismiss it at this time. As mentioned elsewhere, I look upon fever as an index of the patient's vitality and as an index of his ability to react to certain stimuli which are probably of a chemical nature.

Inflammation is accompanied by fever. The changes which take place in inflammation are chemical, and the rise is probably due to the irritation from the products resulting from the chemical change. With this definition we can see that a slight rise of temperature of a few tenths of a degree which accompanies an operative or traumatic wound is probably due to the chemical changes at the site of the trauma. The increased cell activity which takes place is accompanied by production of new chemical substances, whose absorption causes increase in heat production.

When an infection occurs, there is a reaction between the bacteria and the antibodies in the blood. There is also a gathering of leucocytes at the point of inoculation. Many of these leucocytes are destroyed with the liberation of enzymes. Resulting from the changes between the bacteria and antibodies and resulting from the action of the enzymes upon the tissues, there are certain disturbances which occur. Toxins are thrown out, and the body cells respond with increased temperature during their attempt to destroy them.

That this theory of fever being a result of the protective reaction of the body cells in response to chemical substances is correct is to be inferred from both animal experimentation and clinical observation. If an animal is given toxins up to a certain point, the animal responds with an increase of temperature; but if the amount of toxins be increased, instead of a rise, there is

a drop in temperature. As long as the body is able to react and destroy the toxins, it manifests itself by an increase of temperature; but when it gets to a place where it is no longer able to do this, then reaction fails to occur, and the temperature falls. We see the same thing in human beings. A patient with tuberculosis will maintain a high temperature for many months; then, if there is a rapid necrosis with absorption of the products of tissue destruction, the temperature drops. I am inclined to believe that this accounts for the very wide range in daily temperature in that class of cases which we have been wont to speak of as "mixed infection," as well as the type which shows itself when there is a rapid absorption of destroyed lung tissue going on. We have a marked depression of temperature in early mornings, and then, in the afternoons, we have a high elevation. Large quantities of toxins are thrown into the body fluids, resulting in a great depression of temperature; then the body recovers its depression and reacts with an enormous heat production. This fight goes on sometimes for a few days, sometimes for a long time, until either the organism overcomes the toxemia or the toxemia overcomes the organism. Whichever wins, as a rule, the wide variation of the temperature curve becomes narrower. Instead of swinging six or eight, or even ten, degrees a day, as I have seen it, it will narrow down to a degree and a half or two degrees a day. It will assume a high or low level according to the condition of the patient. If the patient is not able to overcome the toxins, the temperature gradually sinks lower and lower until death ensues; if he is able, the curve assumes a higher plane until such time as the inflammatory process quiets down.

I discussed this subject [1] quite fully in a previous paper. I called attention to enzymes as a cause of fever. While I recognize that our knowledge on this subject is not very complete, yet it seems to me to be exceptionally suggestive and worthy of very careful study. Some very valuable observations have been made by Asocli and Bezzola,[2] Müller,[3] K. Meyer,[4] Opie,[5] Hahn,[6] and others.

---

[1] A Study of Fever in Tuberculosis with Reference to its Causation and Treatment, *Journal of the American Medical Association*, September 23, 1911, pp. 1025–30.
[2] *Berl. klin. Woch.*, 1903, p. 391.
[3] Verhandl. d. 20 Cong. f. Inn. Med., 1902, p. 192.
[4] *Berl. klin. Wochenschrift*, 1909, p. 1890.
[5] Report of Sixth Int. Congress on Tuberculosis, Washington, 1908, p. 255, *Journal of Experimental Medicine*, 1911, XIII, No. 1, p. 162.
[6] *Berl. klin. Woch.*, 1897, p. 499.

Our ideas of fever in tuberculosis have been very much confused. Theoretically, for a number of years, many have looked upon fever in tuberculosis as due almost wholly to mixed infection; but when it comes to treating tuberculosis, most clinicians have assumed that the fever is due to tuberculin, or, at least, that the system is surcharged with tuberculin during the period of fever. That this latter is not true is susceptible to theoretical proof and practical demonstration. Quoting from my former paper:

> The reason usually assigned for the non-employment of tuberculin in fever is that the patients are already saturated with tuberculin. That this is not necessarily true can easily be established. In the first place, it is probable, as mentioned above, that tubercle toxins are not the chief factor in the production of fever. Again, as noted in a previous paper, if the system of the fever patient were completely saturated with tuberculin, all foci would be the seats of focal reactions which could be easily detected in all visible tuberculous processes, such as ulcerations of the larynx and pharynx. But this is not true. Such processes show the focal reactions, however, after injections of therapeutic doses of tuberculin, which, in amount, are short of a fever reaction. Still again, if this were true, all tuberculous foci would break down as a result of the constant focal reactions. Furthermore, if the patient were saturated with tuberculin, the temperature would fall; for excessive doses of toxins would overcome the patient's reactive powers and cause a drop in temperature.

Mixed infection is a condition about which we know very little; not nearly so much as might be inferred from the frequency with which it is discussed in literature. Koch [7] declared that a daily temperature curve of 100.4° in a case of pulmonary tuberculosis is due to septic micro-organisms and consequently not suited to tuberculin treatment. This statement was accepted by the profession generally, and unfortunately, it still appears in current literature, although we know that it is not true. There are many cases of fever in tuberculosis that are what we might call purely tuberculous, in which the curve runs very high —for example, those of acute miliary tuberculosis (Fig. 5). There are also fevers due to other conditions which I shall indicate later, which do not seem to have any association with mixed infection.

The term "mixed infection" is used very loosely. It is a very common thing for clinicians to examine sputum which has been collected without any care in regard to mouth contamination, and

[7] *Deutsche med. Woch.*, April 1, 1897, p. 201.

without asepsis in regard to the receptacle in which it is collected, and finding certain bacteria in it, consider it a case of mixed infection. There are numerous varieties of bacteria that can be found in the sputum of nearly all patients suffering from tuberculosis; but this does not mean that they are pathological.

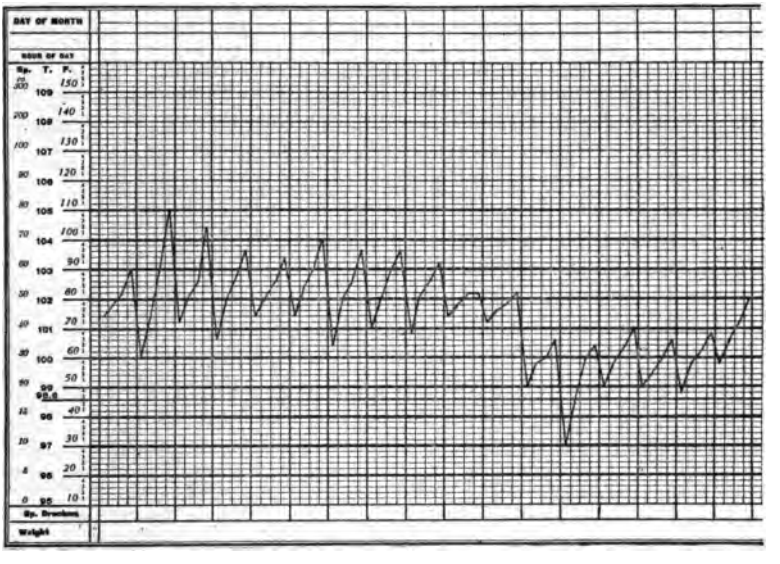


Fig. 5.—Chart of a patient suffering from acute miliary tuberculosis with fatal issue in three weeks. It will be noted that the daily variation is not great, although the temperature was very high as long as the patient was able to react. The drop of temperature near the end indicates the inability of the patient to react to the stimulation of the toxins. Although the case was severe and temperature high, yet daily variation showed absence of autolysis.

When it comes to isolating these bacteria and applying to them the tests of pathogenicity, we find that they do not meet these tests in a very large per cent of cases.

The earlier workers with Koch, particularly Kitasato and Carl Spengler, studied the subject of mixed infection quite carefully. They required, for the bacteria found in the sputum to be considered as causing mixed infection, that they should be found only after the mouth had been thoroughly washed and the sputum had been collected in sterile containers, washed through several waters, and a particle chosen for examination, which sank to the bottom, indicating that it was from a cavity. With this test we find a variety of bacteria in tuberculous sputum; the staphylococcus, streptococcus, influenza bacillus, pneumococcus,

and *Micrococcus catarrhalis* being most common. But even when they are found, after all this care, we are not positive of their pathogenicity. The fact that they are in the cavity does not mean that they are causing the destruction of tissue, or that they are producing symptoms. It may be that they are there in a purely saprophytic capacity, for we find all of these in the mouth and nose, without producing symptoms. Many of our best observers in tuberculosis, among whom I would mention Denys and Béraneck, have receded from their former position regarding mixed infection and now take the view that mixed infection is comparatively rare. While I was formerly a stanch supporter of the mixed-infection theory, I have been led to believe from my clinical observation that it is not so common as is generally thought.

In discussing the treatment of tuberculosis where it is supposed that mixed infection is present, I cannot understand the usual attitude of the profession. Mixed-infection cases are supposed to be unsuitable for tuberculin treatment. No very convincing reason, however, is given for this position. Even granting that the patient is suffering from mixed infection, is not the tuberculous process there just the same and does it not require the same treatment for its cure that it would if mixed infection were not present? That this complication makes the treatment more difficult and more serious does not make it any the less necessary on our part to employ every measure that we know for the patient's benefit. Later I shall discuss more fully the use of tuberculin in the treatment of cases suffering from mixed infection; but here I wish to call attention to the fact that, while the organism is not able to respond in the production of antibodies so well as it is when fever is not present, at the same time if we can, by the successful administration of tuberculin, help, even in a small way, toward relieving the tuberculous process, then it is our duty to do it, of course, endeavoring to combat the mixed infection at the same time. There is no reason for first treating these cases with vaccine before the employment of tuberculin. If they are not able to respond to tuberculin, they will not respond to vaccines. So this argument falls of its own weight. I treat them with both simultaneously.

In the paper mentioned above, in referring to the causes of fever in tuberculosis, I said:

"I believe that the primary causes of fever are at least three in number: the tubercle bacillus and its toxins; associated bacteria and their toxins; and enzymes and products resulting from their action upon the body cells. This last cause is generally disregarded in discussions on this subject; and yet I believe it is a factor of great importance in all cases of advanced tuberculosis of the ulcerative type. I cannot help thinking that one of the greatest dangers to the tuberculous patient arises from the absorption of products resulting from enzyme action."

Probably the chief source of enzymes in the blood is the leucocytes. As they break down, the enzymes are liberated and set free to act. They produce necrosis of the tissues and set free many toxins which must be disposed of by the organism. When the necrotic process is slight, the effect upon the organism amounts to very little, but when it is extensive, as we see it when rapid destruction of the lung is taking place in acute caseous pneumonia or when cavity formation is occurring, it is a factor of very great importance, and seriously taxes the reactive capacity of the patient. In fact, the absorption of the poisons which results from the necrosis of tissue is, to my mind, one of the big factors in the production of ill effects upon patients suffering from advanced tuberculosis.

There have been numerous methods of therapy suggested during recent years, whereby this tendency to necrosis might be overcome. I agree with Hort [8] that the cells of the body must develop an immunity to the toxins produced by the destruction of the pulmonary tissue, just as much as they produce immunity to the tubercle bacillus and its toxins. Some experimenters have used extracts of the patient's own sputum in therapy, attempting in this way to overcome necrosis, and have reported some beneficial results. I would suggest that a valuable field for investigators would be the attempt to make a serum by injecting animals with a pulp made from tuberculous lungs, to see if it would not be possible to produce certain antibodies against the factors which produce the necrosis and against the toxins which result from necrosis. That tuberculin is a big factor in the prevention of necrosis cannot be denied. Any remedy which will lessen the action of bacteria and reduce their virulence is a factor in lessening necrosis. That tuberculin will do this is

[8] Rational Immunization in the Treatment of Pulmonary Tuberculosis, London,

the common experience of all who have carefully studied tuberculin. It has a tendency to increase fibrosis and heal isolated tubercles, thus preventing necrosis and ulceration. Sahli quotes a very interesting article,[9] dealing with some of the work that has been done along these lines, thus:

In addition to their oxidizing action, the leucocytes possess a most important ferment action, a tryptic action discovered by Müller, Kolaczek, and Jochmann, though, strangely enough, Müller and Peisner consider this detrimental to the course of an inflammatory process. They hold that the tryptic leucocyte ferment, collected in large quantities during suppuration, melts away the tissues and aids the progress of the suppuration. Starting from this standpoint, the writers have founded and tested a so-called antiferment treatment of suppurative processes. Normal blood-serum contains an antiferment of this leucocyte ferment; the treatment consists in the injection of the normal serum with a view to restraining the suppuration. It is asserted that favorable results have thereby been obtained, suppuration having been quickly dried up and the tissue destruction reduced to a minimum. When one considers the extraordinary adaptability of the animal organism, it does not seem possible that the tryptic ferment of the leucocytes, otherwise of very real value, can have such a defect. If then, as I do not doubt, the tryptic ferment does cause tissue destruction, is it not probable that in the severe infections, where so large a quantity of leucocytes is produced, this destruction is really advantageous to the organism, as the discharge from the abscess formed totally eliminates the harmful elements? I admit that such a useful arrangement may overshoot the mark, examples of which are frequent in pathology. Reflex muscle contractions are very useful as a means of defense against injury, but bones can be broken in this way. But is it not probable that only those parts of the tissues are destroyed by the tryptic action of leucocytes, which are already doomed to necrotic destruction by the action of bacteria? The favorable action of the antiferment serum injected may not depend on its antiferment content; it may simply be equivalent to the injection of normal serum into the inflamed tissues, bringing to the point of action what I have called inflammatory antibodies which help to neutralize the toxin. Such antibodies are indeed supplied in the exudation fluid, but perhaps in insufficient quantity. May not, then, this so-called antiferment treatment be merely a kind of serum treatment with normal serum, analogous to that which I have recommended for therapeutic trial in general infections in the form of subcutaneous injections of large quantities of normal human serum? A suggested method of treatment is found in the *Corres.-Blatt für Schweizer Arzte*, No. 20, 1909.

If it be objected that the ferment must also serve some useful purpose, I naturally agree, but must point out that this could not be if, in the inflammatory process, the ferment and antiferment simply neutralized each other. In this case nature would have dropped the proteolytic ferment. The antiferment

[9] *Corres.-Blatt fur Schweizer Arzte*, No. 20, 1909.

action is clearly not directed to the process of inflammation but to the circulating blood where, indeed, the tryptic action of the leucocytes must be suppressed in the interests of the organism, since no useful end can be served by an autodigestion of the blood.

CHAPTER XI.

TEMPERATURE CURVE IN TUBERCULOSIS.

Any discussion of this subject, to be of value, must be based upon accurate measurements. It is not sufficient to use any thermometer that the patient happens to possess or to hold it carelessly for an unmeasured time; but if the temperature curve is to be of any value, it must be registered by an accurate thermometer in an exact manner as mentioned on page 25. If the temperature is taken in this manner, we shall find that the curves in tuberculosis can be classified to a certain extent, according to the pathological condition present.

Normal Curve.—A great deal of anxiety is often felt on the part of patients by a misunderstanding of the daily variations in the normal temperature curve. They are apt to think that they should have a temperature of 98.6° at all hours of the day. I might add that the natural temperature variation is not entirely appreciated by physicians. There is a daily variation of a degree or a degree and a half in the normal temperature curve. The temperature is lowest in the early morning, usually about four or five o'clock; and highest, as a rule, some time in the afternoon. By seven or eight o'clock the morning temperature is already rising; so a mouth temperature of 97.4° or 97.6° at this time is normal. From the early morning there should be a gradual elevation, until some time later in the day when the normal is reached. It may be some time before noon, or it may be some time later. The accompanying chart (Fig. 6) from Jürgensen showing the rectal temperature, which is about a degree higher than that for the mouth, shows this normal variation. It is necessary to understand this normal variation if we are to appreciate the changes which occur in the curve in tuberculosis. Especially is this necessary when we watch the variations in the curve as closely as we do in the administration of tuberculin.

While I am very desirous that the physician should not pay attention to the temperature curve to the neglect of other symp

toms which are indicative of tuberculin action, yet he must understand the normal curve and the variations which occur in it, as well as the peculiar variations which take place in tuberculosis, if he desires to administer tuberculin accurately.

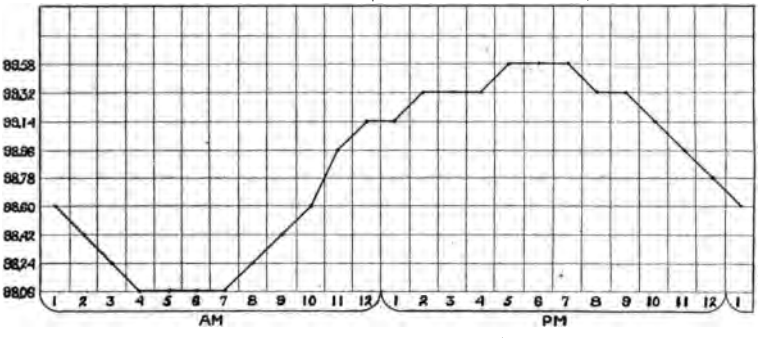


Fig. 6.—Illustrating the daily variations in temperature (rectal) under normal conditions (Jürgensen). It will be noticed that the normal temperature has a daily variation of about one and a half degrees between the maximum and minimum.

Try as we may, in the therapeutic administration of tuberculin, it is impossible to divorce ourselves from the study of the temperature curve.

Temperature Curve in Tuberculosis.—I do not mean to indi-

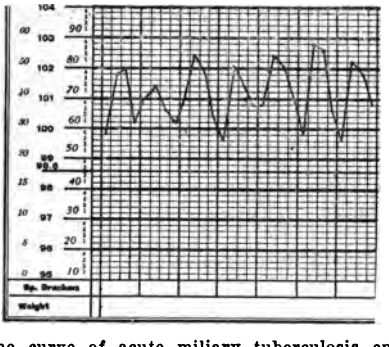


Fig. 7.—Illustrating the curve of acute miliary tuberculosis engrafted on a chronic process. It will be noticed that the entire curve is raised, the daily variation being about the same as that which occurs in a chronic tuberculosis of moderate activity. The miliary condition does not increase the daily variation.

cate that tuberculosis is accompanied by any particular temperature curve by which we can rule out other conditions; but in pure tuberculosis we find that the daily variation of a degree or a degree and a half is not disturbed to any extent. If the

temperature is reaching 99° in the afternoon, we shall usually find that the morning temperature has also become slightly elevated. We usually speak, under such conditions, of a patient

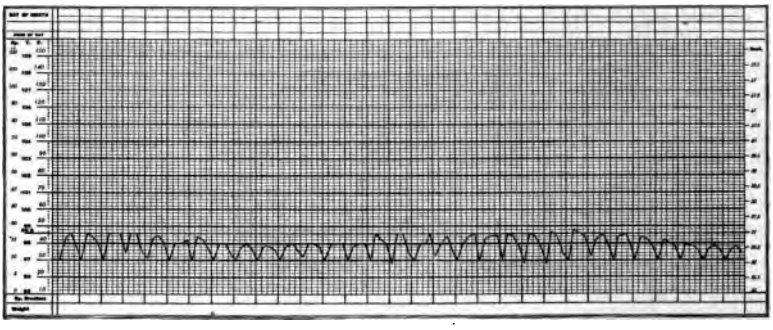


Fig. 8.—Illustrating the temperature curve of slightly active, early pulmonary tuberculosis. It will be noticed that the curve goes in waves, a number of days up, and a number of days down, etc. It will also be noticed that the daily variation is about normal, showing that autolysis is not a factor.

having a little rise in the afternoon. The patient has just as much of a rise in the early morning. In pure tuberculosis, as we find it in early lesions, also in many chronic quiescent lesions of both the ulcerative and fibroid type, and in cases of acute

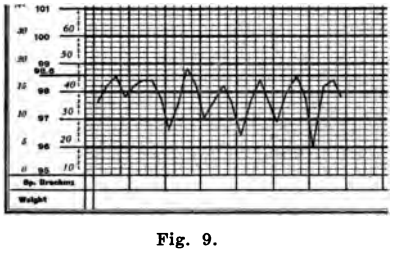


Fig. 9.

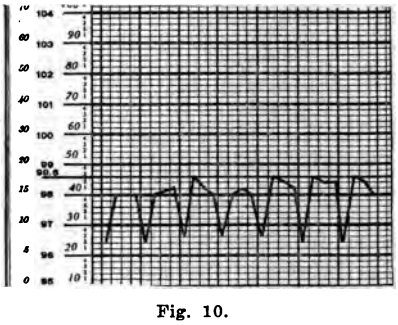


Fig. 10.

Fig. 9.—Illustrating the fever curve of chronic fibroid tuberculosis. It will be noticed that the daily variation in the curve is about normal, consisting of about a degree and a half's difference between early morning and afternoon. Autolysis not a factor.

Fig. 10.—Illustrating curve of quiescent tuberculosis, ulcerative type. It will be noticed that the daily variation is not far from the normal, the morning temperature is a little lower than normal, while the daily maximum approaches normal. Autolysis not a factor.

miliary tuberculosis (Figs. 7–10), we find very often that the normal daily variation of the curve is not markedly exaggerated. The point that I wish to make clear is that in active tuberculosis

commonly the whole curve is raised, the morning as well as the afternoon temperature. A temperature of 99° in the afternoon, in early, in chronic quiescent, ulcerative, or in fibroid tuberculosis is nearly always accompanied by a morning temperature of 98°, or slightly under 98°; a temperature of 99½° in the afternoon by a morning temperature of 98 or 98½°.

Temperature Curve as Affected by Autolysis.—That tuberculosis does not remain a simple inflammatory process long is well known. The tubercles soon take upon themselves pathological change which results in softening. While this softening is due indirectly to the tubercle bacilli, it is probably directly an enzyme action; therefore I speak of the fever as due to the

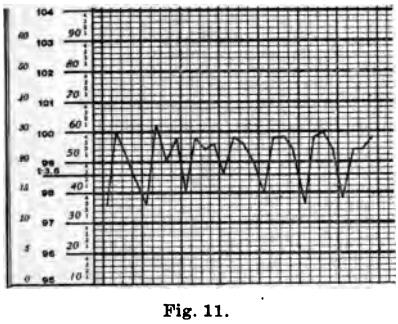


Fig. 11.

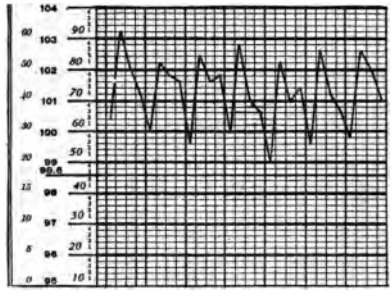


Fig. 12.

Fig. 11.—Illustrating curve of moderate activity in tuberculosis of chronic ulcerative type. It will be noticed that the entire curve is raised; the morning being above normal for the morning, the same as the afternoon is above normal for the afternoon. Aside from this, the daily variation is also increased because of necrosis. Autolysis a slight factor in this curve.

Fig. 12.—Illustrating curve of caseating pneumonic type. The entire curve is raised, the morning temperature being high as well as the afternoon. The daily variation is somewhat more than normal, showing a moderate degree of autolysis.

absorption of the products of autolysis (albumoses). This fever is due to the process of absorbing and rendering innocuous the tissue of the tubercles which have softened and broken down. As soon as this process begins the daily variation in the temperature curve increases. The difference in the curve in the morning and afternoon is a little bit greater. It may take upon itself a variation of two degrees; in fact, two or two and a half degrees is a very common oscillation in tuberculosis with a moderate degree of autolysis. This represents the usual curve during moderate activity (Figs. 11–13); but if a great amount of tissue is involved in the necrotic process, and if the body cells are

called upon to take care of a great deal of broken-down cellular tissue (albumoses), then we find that the swing of the temperature curve becomes very great (Fig. 14). We see it sometimes vary as much as ten degrees in a single day. From the great amount of the products of autolysis which are taken up by the blood-stream, the action of the body cells is, for a time, depressed. Resulting from this, we have a very low temperature in the early mornings; but the cells recover, and later in the day, they rise to the occasion, regaining their reactive powers and

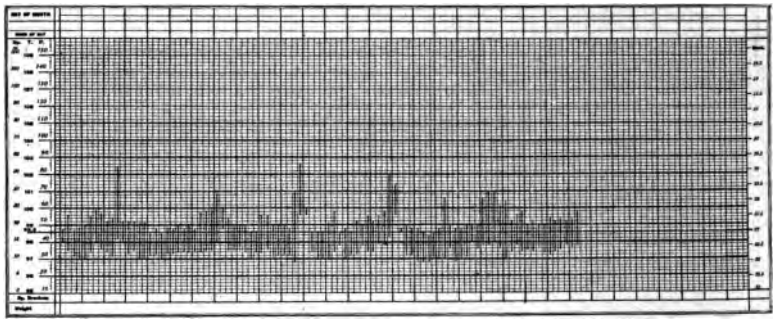


Fig. 13.—Three months' curve illustrating a moderate degree of autolysis. It will be noticed that there were high periods of temperature at intervals of a little more than two weeks during the entire period. At these times the maximum for a day or two usually ran very high. These were usually associated with increased cough and expectoration, the result being cavity formation. It will also be noticed that the daily range of temperature varies considerable, showing, as a rule, however, about two degrees, thus indicating a moderate degree of autolysis. At the time of the temperature spells, however, it will be noticed that the variation becomes greater, being three degrees or even four degrees in some instances.

This chart, together with the last two charts in the book, is made in such a manner that each line represents the entire daily variation of temperature.

responding to the production of heat and elevation of the temperature curve often to 103° or 104°, and even 105°.

The clinical symptoms which are present at this time, aside from the fever, are those of profound intoxication, malaise, aching, disturbance on the part of the digestive system, nervousness, chilliness, rigor, and often extreme weakness and mental depression. There is also usually an increase on the part of all the symptoms directly dependent upon the disease within the lung.

Curve in Mixed Infection.—The curve in mixed infection is not unlike the one just described (Fig. 15). The curve dependent upon the absorption of the products of autolysis has two factors in its production: the tubercle toxins, and the albumoses absorbed from the areas of necrosis. The mixed-infection curve

has three processes: the tubercle toxins, the associated bacterial toxins, whatever they may be, and the albumoses from the tissue necrosis. Thus it can be seen that the curve in mixed infection is not unlike the one just mentioned. All of the phenomena which are found present in connection with the autolytic curve are found in the mixed-infection curve. Marked depression in the temperature in the early mornings with a high rise in the afternoon, rigor, the clinical symptoms of malaise, aching, and severe prostration mentioned in the fever due to autolysis are also present. While the conditions mentioned above produce

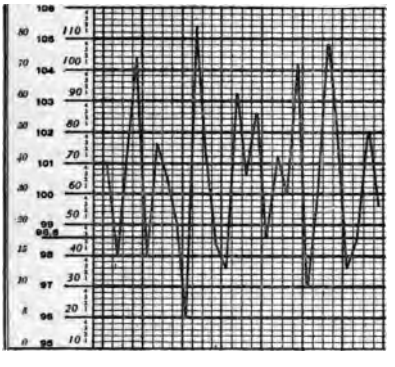


Fig. 14.

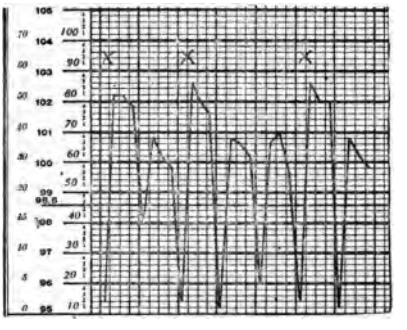


Fig. 15.

Fig. 14.—Illustrating marked autolysis, rapid disintegration of lung tissue with absorption of large quantities of toxins, the body cells still being able to react. Wide variation in daily temperature is noticed, amounting in one day to more than nine degrees.

Fig. 15.—Illustrating the curve of mixed infection. Not only is the morning temperature much below normal, but the afternoon temperature is considerably above normal, making a wide daily variation. Tubercle toxins, associated bacteria and their toxins, and autolysis, all factors in the production of this curve.
This curve also illustrates the effect of baths in raising temperature as described on page 143. Baths were given on the days marked by crosses.

certain types of curves, there are innumerable conditions which come in and change the daily variation.

Cause of Chill or Rigor.—In this connection it is well to discuss the chill or rigor, together with the great depression of the temperature curve as it occurs in the cases just mentioned. Chill or rigor usually occurs in the early morning. How to account for it is not wholly clear. As mentioned above, this is the time of day when the temperature is usually lowest and when many toxins are being thrown out into the body fluids. In the conditions just mentioned, toxins enter the blood-stream in the

greatest numbers in the early morning when the patient awakens and the bodily activities begin; so the most favorable conditions for the depression of the temperature curve are present at that time. Bearing in mind that an excessive amount of toxins lowers the temperature and that a reaction on the part of the body cells causes elevation of the temperature curve, we can see that ideal conditions are present for a wide oscillation.

As a result of a rapid discharge of the toxins into the blood-stream in the early morning, there is a rapid fall of temperature and a call on the part of the organism for increased heat production. The body responds with a rigor. The greatest source of heat production in the body is muscular activity; consequently the organism takes advantage of this, and when called upon for a rapid production of heat, throws the muscles into rapid contraction, producing what is known as rigor.[1] Its purpose is the rapid production of heat, and it results in a quick response, as shown by the temperature curve, which, as a rule, goes far above normal. Coincident with this heat production on the part of the muscles, it is probable that there is also an increase in the tone of the body cells and an increase in their capacity to take care of the toxins with which the body has been surcharged, in consequence of which there is an additional factor in the rapid production of heat and a high elevation of the temperature curve. Rogers says: "It (moderate hyperthermia) stimulates the activity of the leucocytes, as was shown by Dr. Maurel, and it increases the germicidal power of the blood, as has been demonstrated by Kast, Henrijean, and Rovighi."

That the chill is a response on the part of the body to the demand for more heat can be inferred from two factors which produce it. Chill may be produced as a result of a great amount of toxins. It may also be produced by the surface of the body becoming rapidly cooled, as we note it in the early morning. It is a common experience in cold weather that patients neglect putting on sufficient clothing when they first arise for the day. They become chilled and after a time have a distinct rigor, which is followed by heat production and an elevation of the temperature curve. Thus, a little negligence in the early morning spoils the entire day for the patient.

It might be thought that a discussion of these advanced con-

[1] Rogers: Infectious Diseases, Lea and Febiger, Philadelphia, 1903.

ditions should have no place in a monograph on tuberculin, but I have for years treated all such cases with tuberculin along with all other measures; and if I can make clear what is producing these temperatures and show that they are not due to tuberculin, as has been so long assumed, my argument can be better understood; and while, as I insist elsewhere, those without experience in tuberculin therapy should not treat these cases, yet I feel sure that they can be helped, if help is possible, by its proper employment. It should only be undertaken, however, in institutions by experts. Even in advocating tuberculin with these strictures, I know that I am laying myself open to criticism; my only answer is—I can show the results. These patients do not react to tuberculin so readily as the literature would lead one to believe. They are comparatively insensitive. Inasmuch, however, as strong focal reactions seem undesirable, I usually advance more slowly and never carry the doses so high as I do in less severe cases (pages 181, 202–211).

Factors Interfering with the Regular Curve.—Anything which causes an extra amount of heat production or an extra amount of heat loss, or anything which interferes with the dissipation of heat, will produce extra change in what I have described as the normal curve of tuberculosis, the curve of autolysis, and the curve of mixed infection. For example, when a patient eats a hearty meal, there is a great amount of food which must be oxidized rapidly. The result is that there is a rise in the temperature curve immediately following. This is noted very often in the temperature record taken immediately after meals; and in institutions where the heavy meal is usually given in the evening, but changed to the middle of the day on Sundays and holidays, a rise after this midday meal is the rule. This amounts to from a few tenths to a whole degree. A rise of one-half degree is a very common experience following the noonday meal, even on ordinary days. A bath will also change the temperature curve. Very commonly following a bath, there is a failure on the part of the patient to react. A chilling of the surface with a temporary depression of the temperature curve takes place. This chilling of the surface, however, results in checking heat dissipation. The result is that after a little time the temperature rises higher than it has been on preceding days. (This is shown in Fig. 15.) Very often where rest hours are observed in

the afternoon and the patient covers himself up and goes to sleep, he will awaken with a higher temperature than is usual with him when he does not cover up and go to sleep. He often interprets this as an argument that he should not go to sleep. The proper explanation of it, however, is that, by being covered, the heat dissipation has been checked, resulting in a temporary elevation of the curve. It is nothing serious and passes off in a few minutes after the patient is up and around. Thermic disturbances have a very marked effect on the temperature curve, as is shown in Fig. 16. On cold days the natural curve

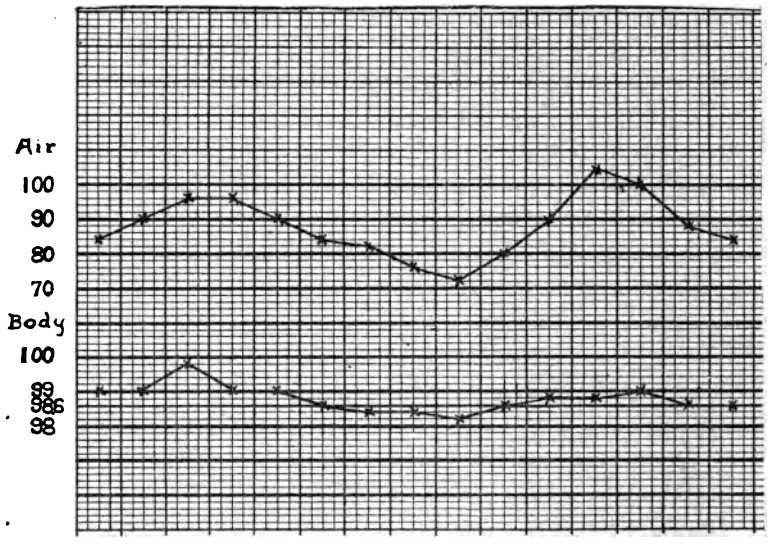


Fig. 16.—Illustrating the influence of atmospheric temperature on body temperature. Lower curve, body temperature; upper curve, atmospheric temperature.

of the patient is usually depressed from one or two tenths to half a degree, and on hot days the curve rises to about the same extent. Sometimes a difference in temperature is noted on the two sides of the mouth, it being several tenths higher on the side of greater activity. This is due to the greater vasodilator effect on that side, causing more blood to be present. In one case which I studied carefully for some time the rectal temperature and mouth temperature on the side of involvement were almost identical. I have also noticed that mouth temperatures are sometimes a little higher when the patient lies down

than when he sits up, the difference probably being due to the difference in the amount of blood in the mouth on account of gravity.

It is very necessary to understand the explanation of these variations. I have found it to make a great difference in my interpretation of the curve, and it is essential to interpret the temperature curve correctly if it is to be taken as a guide for the administration of tuberculin. For example, suppose that a dose of tuberculin is given on a day when the patient is given a bath and the bath is accompanied by a slight rise of temperature —the wrong interpretation would consider that the rise was due to dosage. Suppose that the patient has not been in the habit

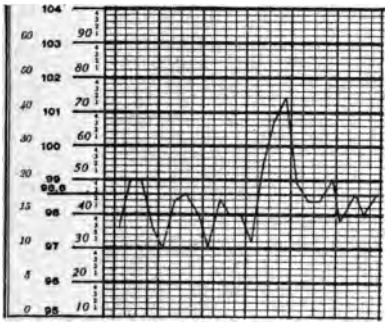


Fig. 17.

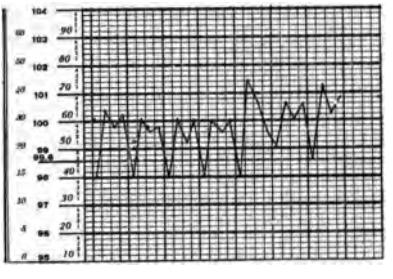


Fig. 18.

Fig. 17.—Illustrating the effect of overexertion in a chronic inactive case of pulmonary tuberculosis. Prompt return to normal.

Fig. 18.—Illustrating the effect of overexertion in chronic active tuberculosis. Failure to return to normal.

of sleeping and lies down and covers himself up and takes a nap, and the temperature is higher on awakening—this also might be interpreted as being due to a reaction. The same thing is true on warm days. The same thing is true of the rise following the heavy Sunday meal, as mentioned before. But these are only a few of the many things which affect the curve.

Physical and Mental Exertion.—Another factor which seems to be fairly generally understood is physical exertion. Physical exertion will produce a rise in the curve of a tuberculous patient. This varies according to the condition present and according to the patient. In some instances the curve is very sharp, the temperature rising several degrees and dropping within a day or two, as shown in Fig. 17. In others it rises gradually and

produces certain definite disturbances in the areas of involvement, which do not right themselves for a long time (Fig. 18). It is easy to see how, by physical exertion, more toxin could be thrown out into the blood-stream, causing an autoinoculation with a rise of temperature. It is also easy to see how, by exer-

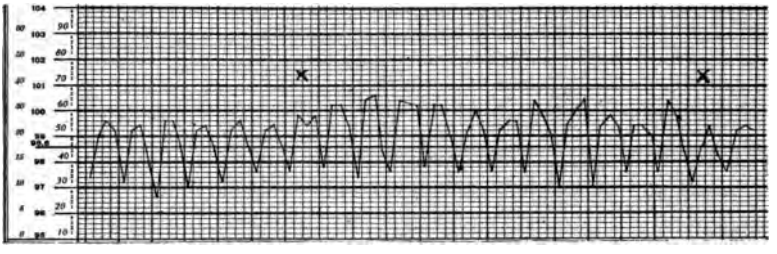


Fig. 19.—Illustrating effect of worry in patient suffering from chronic active tuberculosis. On the day marked by first cross the patient received word that her mother was suffering from cancer. On the day marked by second cross the patient received word that the diagnosis was incorrect, and this marks a prompt drop in temperature.

tion, the muscles themselves could produce an extra amount of heat and cause some rise in the temperature curve; but to understand how mental exertion will cause an elevation in the temperature is more difficult. That the temperature curve is altered very materially by the mental state is well known, but personally I am not able to satisfy myself fully as to how this is produced (Fig. 19). Joy, sorrow, worry, deep thought, reading, playing

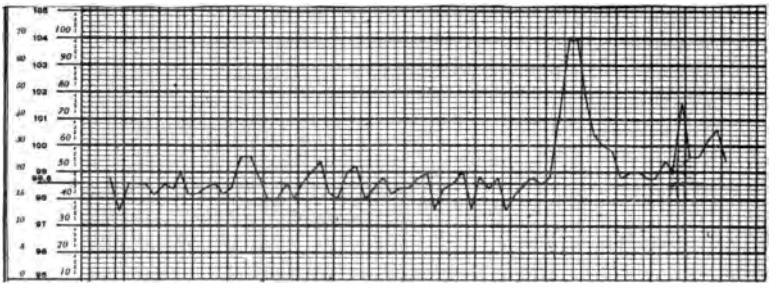


Fig. 20.—Illustrating the temperature disturbance produced by an attack of acute gastroenteritis, in a patient who was suffering from early active tuberculosis.

games—such as cards, chess, checkers—conversation (in this there may be a physical as well as mental basis), or the prolonged strain due to visiting, when one is not accustomed to it, are all known to affect the temperature curve. Whether this is due to

its effect on the heat center or the vasomotor system, I am unable to decide.

Other factors which produce change in the temperature curve are indigestion (Fig. 20), constipation, diarrhea, menstruation, and intercurrent infections—such as cold, bronchitis, la grippe, pneumonia, pneumothorax, pleurisy, and angina. The importance of these variations in the temperature curve will be seen when I discuss it with reference to tuberculin treatment.

Premenstrual Fever.—Observing a great many female patients has shown us that the temperature curve goes in waves. There is a high wave and a low wave. The change in this wave is usually determined by menstruation. Preceding menstruation,

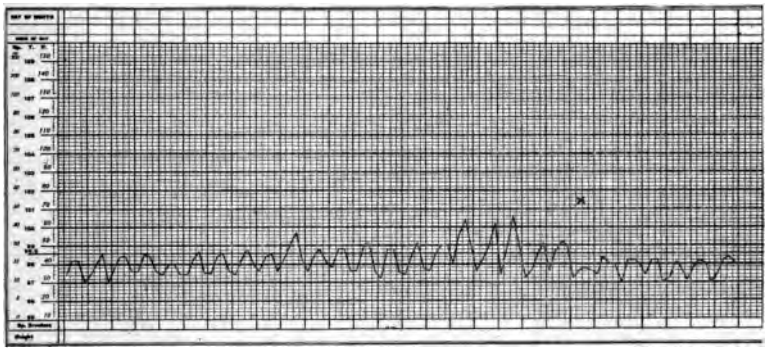


Fig. 21.—Illustrating premenstrual rise in temperature curve. Prompt drop on day of menstruation. Patient suffering from chronic ulcerative tuberculosis, moderately active.

the entire curve usually takes a higher plane (Fig. 21). If the patient has been running a normal temperature of from 97½° to 98½°, when this rise comes on, which occurs anywhere from three or four days to two weeks preceding the beginning of menstruation, the curve shifts say from 98° to 99°. There is usually a difference of about half a degree in the curve during this time. When menstruation comes on, as a rule, the temperature drops promptly again. This premenstrual rise is often not a simple rise of half a degree, but as I have often seen, it will in some instances amount to several degrees. I have seen women, who were running practically a normal temperature, begin several days, probably a week, before the period time to have an increase in all their symptoms. The cough will increase; expecto-

ration will increase; the patient becomes more nervous; the appetite decreases; insomnia may be present; and the temperature and pulse curves rise. Then the symptoms subside coincident with the day on which menstruation begins.

Contrary to this rule, there is sometimes a menstrual temperature. The curve may remain at its normal level until menstruation begins; then a rise will occur which may last a few days or a number of days.

These changes in the curve are very interesting, but the premenstrual rise does not seem to be confined, as we formerly thought, to tuberculous patients. It seems that many of those who are not tuberculous show this same monthly change. This must be kept in mind in interpreting the temperature chart where tuberculin is being employed. Otherwise, should a dose be given on the day of the rise, it might be interpreted as a reaction.

Characteristics of the Temperature Curve Due to Tuberculin Reaction.—Since there are so many things which cause elevations in the temperature curve in tuberculosis, it is difficult at times to determine whether or not the injection has produced a given rise which may occur on the day that it is given. Where doses are being given with intervals of one or two days to a week between them, they are sure to fall on days, every now and then, when the temperature rises from some of these other causes, and it is necessary for the physician to be fairly accurate in his interpretation in order to avoid errors.

The rise in temperature caused by the tuberculin assumes two forms: one coming on at once; another, a secondary reaction, coming on a few days after the dose has been given. The rise coming on at once differs somewhat according to the preparation used. It comes on sooner with human tuberculin than with bovine. In the former it usually appears the same day if the dose is given in the morning; while with bovine it usually comes on the second day. As a rule, a rise which starts two or three hours after an injection is not due to the remedy, although we see it beginning very often about eight, and sometimes six and even four, hours after the dose has been administered.

Another characteristic of this curve is that it does not reach its normal on the morning of the second day (Fig. 22). If a

fever reaction occurs on one day as a result of an injection of tuberculin, the early morning temperature on the succeeding day is nearly always above the normal for that time of day. While

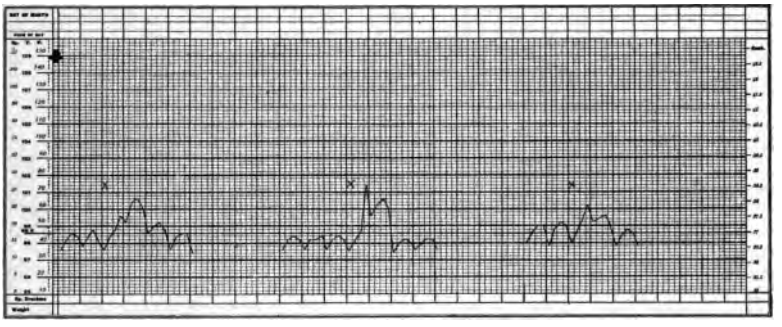


Fig. 22.—Illustrating three different curves representing tuberculin reactions. It will be noted that the temperature does not return to normal on the second day of the reaction. This is quite characteristic of the curve of tuberculin reactions. Time of dose is marked by "x."

this occurs in other conditions which produce rise of temperature, it is the rule after tuberculin.

The secondary reaction usually comes on a few days after

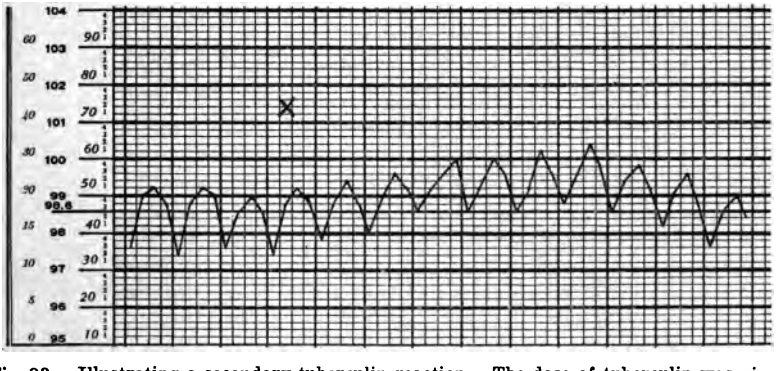


Fig. 23.—Illustrating a secondary tuberculin reaction. The dose of tuberculin was given on the day indicated by the cross. Temperature showed only a slight rise the second day, but did not reach its maximum until the third, fourth, fifth, and sixth days. It will be noticed that this rise designated as a secondary reaction is similar to the rise that often occurs in active tuberculosis (see Fig. 24) as a result of inflammation in the tuberculous areas. It is possible that it might be due to a focal reaction.

the dose (Fig. 23). It is probably a result of a focal reaction. It should be respected; for if the focal stimulation is pushed at this time, serious results might follow. The characteristic of

the temperature curve due to a secondary reaction is a slight elevation of the entire curve, just the same as that which ac-

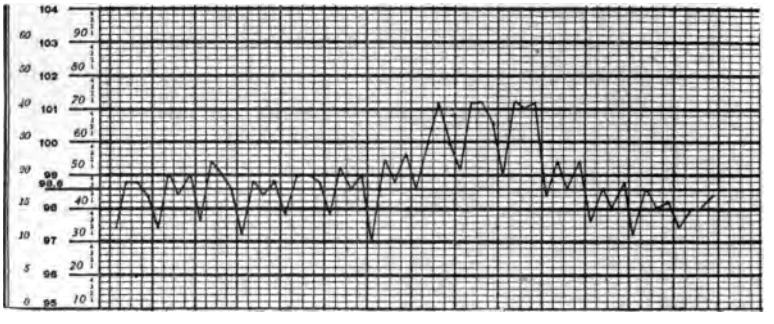


Fig. 24.—Illustrating acute inflammation with expulsion of tuberculous material, in a patient suffering from chronic, slightly active tuberculosis. This is a very common occurrence in active tuberculosis.

companies the natural increase of inflammation that occurs every now and then in tuberculosis; in fact, it cannot be differentiated from it (Fig. 24).

CHAPTER XII.

TECHNIC OF ADMINISTERING TUBERCULIN.

The successful administration of tuberculin depends on giving extra care to minutiæ. There must be a thorough co-operation between patient and physician. The patient must use extra care in keeping and recording symptoms. The physician must use extra caution in interpreting symptoms and signs, and also in administering the remedy. No matter what his knowledge of tuberculin and tuberculosis, no matter how carefully he observes his patient, he will succeed or fail in the therapeutic employment of tuberculin in proportion to the care with which he follows out a carefully developed technic.

Choice of a Preparation.—There is a great deal of misunderstanding about the various preparations of tuberculin. They differ in their method of preparation and also in their chemical content, but all of them have distinctly specific properties and can be used successfully in combating tuberculosis.

I have already mentioned the theory of Wolff-Eisner (page 4), who claims that the action of tuberculin is due to its content in tubercle protein and that the active principle of the various preparations is the same, but differing in amounts; therefore showing that tuberculins differ quantitatively not qualitatively. It seems that this is probably true to a certain extent; nevertheless there are probably different proteins in the tubercle bacillus, as mentioned elsewhere. These various proteins seem to have the same general action, yet differ to some degree. It would seem that, this being true, a combination of all the proteins of the tubercle bacillus would give the best immunizing agent. The preparations on the market may be divided into three classes according to the toxins which they contain: those containing only extracellular toxins; those containing only intracellular toxins; and those containing a combination of both. I prefer on theoretical grounds, as well as from practical experience, to use, for the most part, those belonging to the latter

classification. I believe that they come the nearest representing the tubercle bacillus in its entirety. It is probable that, if we could obtain the tubercle bacillus in solution in its entirety, we should have the ideal preparation as far as therapeutic principles are concerned.

Those products which consist of the culture broth on which the bacilli grow contain certain products which are useless to the remedy, and it has been thought that the protein from the broth might produce some of the reactions which result from the administration of these preparations; therefore, there has been an albumin-free tuberculin produced during recent years. In fact, Koch, himself, gave considerable attention to the production of this product. Whether it will have any particular advantage or not remains to be seen.

I have often said, and wish to emphasize here, it is not so much the tuberculin used, but the method in which it is used, that produces results. It is far better for a physician to familiarize himself with one or two preparations and learn to administer them well than to have a smattering of a dozen preparations and be unable to get the best out of any of them. I would advise those who are attempting to use tuberculin to familiarize themselves with very few preparations, but learn them thoroughly.

It is useless to burden a small monograph in giving a description of all the various preparations of tuberculin. There have been so many made in recent years that it would be confusing and result in little good to even attempt to mention them all. Suffice it to say that any preparation which contains the specific products of the tubercle bacillus is one of value in the treatment of tuberculosis. The relative merits of the preparations would depend very largely upon the man describing them; and this, in turn, would depend very much upon the success which he, individually, has had in the administration of the various ones. One person might understand one preparation much better than another and consequently get better results from its use. He naturally would ascribe the difference to the superior merits of the preparation.

One factor to bear in mind in choosing a preparation is its solubility. Those preparations which contain soluble toxins are absorbed more quickly. They soon leave the tissues at the point of injection, are taken up by the circulation, and in this way

are more apt to produce a general reaction than those preparations which are less soluble and slower of absorption. On account of this, such preparations as T.R., B.E., P.E., together with Watery Extract (von Ruck), T.B.V., P.V. Spengler, and Tuberculin Béraneck, and others belonging to this class, are to be preferred. Especially is this true in all cases where a general reaction is undesirable.

Preparations Which Are Most Commonly Used.—Belonging to the first class—those consisting of extracellular toxins—are Old Tuberculin (O.T.) Koch; Bouillon Filtrate (B.F.) Denys; Perlsucht Tuberculin (P.T.O.) Spengler. Of the preparations belonging to the second class, those containing the intracellular toxins, I would mention Tuberculin R. (T.R.) Koch; Bacillus Emulsion (B.E.) Koch; Perlsucht Emulsion (P.E.) Spengler. Belonging to the third class are Tuberculin Béraneck; Watery Extract, von Ruck; and T.B.V. and P.V. Spengler. It is quite common with some physicians to combine B.F. or O.T. or P.T.O. with T.R. or B.E. or P.E. There are many other preparations which I might mention, but these are the ones that are in common use and are sufficient to use in the illustration of tuberculin therapy. I, personally, have had experience in the use of all of them except Tuberculin Béraneck, and prefer to discuss them on that account. The fact that many other worthy preparations are not mentioned is not to be considered as a discrimination against them. I am discussing principles rather than preparations.

The following is a description of the preparations just mentioned, taken with slight changes from my paper on Tuberculin in Hare's Modern Treatment, page 579, 1910:

Old Tuberculin (O.T.), Koch's original preparation, is the beef broth, containing 5 per cent of glycerin, slightly alkalinized, upon which human bacilli have grown for a period of from six to eight weeks, filtered and treated by boiling for an hour, and then concentrated over a water-bath to one-tenth its volume. It is a variable product, depending on the virulence of the strain of bacilli, the development of their growth, and the medium upon which they grow. It contains 50 per cent of glycerin. The initial dose is 0.001 to 0.1 milligram. Maximum dose is 1 cubic centimeter = 1000 milligrams.

Bouillon Filtrate (B.F.), Denys, is the bouillon culture of human tubercle bacilli filtered through porcelain. It is neither concentrated nor has it been subjected to heat. Denys claims that it is more active than O.T., because the latter has been deprived of some of its active principles by heating. The

initial dose is from 0.0001 to 0.01 milligram. Maximum dose 1 cubic centimeter = 100 milligrams.

Perlsucht Tuberculin (P.T.O.), Spengler, is a filtered bouillon culture of bovine bacilli, concentrated in an incubator, at 37° C. to one half of its original volume. It is then restored to its original volume by the addition of glycerin. One cubic centimeter = 100 milligrams of P.T.O. The initial dose is from 0.0001 to 0.1 milligram. Maximum dose is 1 cubic centimeter = 100 milligrams.

Tuberculin Béraneck is a 20 per cent solution of equal parts of an unheated precipitate, caused by the action of 60 per cent alcohol upon a culture of tubercle bacilli grown upon a special unneutralized medium containing glycerin, but no peptone, and an extract made by treating tubercle bacilli by a 1 per cent solution of orthophosphoric acid. The preparation contains both the intracellular and extracellular toxins. Those who have had experience in the employment of this preparation are convinced that it is less toxic than O.T or T.R. The initial dose is 0.05 cubic centimeter $\frac{A}{128}$ to 0.05 cubic centimeter $\frac{A}{520}$. Maximum dose 1 cubic centimeter strongest solution.

T.B.V. and P.V., Spengler, are preparations containing both the intracellular and extracellular toxins, the former being made from cultures of human bacilli and the latter from cultures of bovine bacilli. The bacilli from which these preparations are made are grown upon a special medium. The initial dose is 0.00000001 to 0.0000001 milligram. Same in febrile cases. Maximum dose .01 milligram.

Tuberculin R., Koch, is an emulsion made from living virulent human tubercle bacilli, which have been ground in a mortar and first extracted by water. It is standardized so that each cubic centimeter contains 10 milligrams of solid substance. The initial dose is 0.0001 to 0.0002 milligram of the solid substance; in febrile cases 0.00001 to 0.00002 milligram. Maximum dose 20 milligrams.

Watery Extract, von Ruck, is made by extracting with water the pulverized bodies of bacilli, which have been previously washed free from culture-fluid with water, and then extracted with alcohol and ether for the purpose of removing fat. The initial dose is 0.001 to 0.01 milligram solid extract. Maximum dose 1 cubic centimeter original solution, 10 milligrams solid extract.

Bacillen Emulsion (B.E.), Koch, is a glycerin emulsion of living, unheated, virulent, human tubercle bacilli pulverized, containing 5 milligrams of solid extract to each cubic centimeter. The initial dose is 0.00001 to 0.0001 milligram solid substance. Maximum dose 5 milligrams.

Perlsucht Emulsion (P.E.), Spengler, is a glycerin emulsion of crushed bodies of bovine bacilli made in the same manner as B.E. The initial dose is 0.00001 to 0.0001 milligram solid substance. Maximum dose 5 milligrams.

Bovine Tuberculin.—Bovine tuberculin was introduced into practice by Carl Spengler, of Davos, Switzerland. Spengler spent several years working in the laboratory with Professor

Koch and is one of his followers to whom part of the honor for the final establishment of tuberculin belongs. When Koch made his announcement at the London Congress that bovine and human tubercle bacilli are different, Spengler had such confidence in the statement that he injected himself at once in the thigh with a large dose of virulent bovine bacilli, the result of which was a localized ulcer which healed after a time without any extension to other parts taking place.

Spengler developed the idea that bovine and human tuberculosis are comparable to smallpox and cowpox, that bovine bacilli are not readily transmitted to man, and that human bacilli are not readily transmitted to cattle, and further, that when present they work in opposition to each other. From this he drew the deductions that human tuberculosis is best treated with bovine tuberculin and vice versa. As a result of his efforts bovine tuberculin has been thoroughly introduced into the therapy of tuberculosis.

There is no question but that bovine preparations of tuberculin are different from human preparations and that their action is somewhat milder. Bandelier and Roepke say: "Bovine is undoubtedly much less toxic and works more gently than the corresponding tuberculin of human origin." Raw, of Liverpool, has had an extended experience with bovine tuberculin in England. The writer was probably the first to use it in America, and after a large experience, has come to use it more and more.

Method of Administration.—The original method of administering tuberculin was subcutaneously. It can be used in any way in which it can be brought in contact with the tissues of the body. It may be injected immediately under the skin, deep into the muscles, or directly into the tuberculous focus, when accessible. It may be used intravenously, by inunction, by inhalation, or by mouth. The inexactness of the last three methods, however, practically precludes their general employment. Furthermore, I see nothing gained by giving tuberculin by inunction, inhalation, or by the mouth. The only reason why it might be suggested is because of the fact that it is painless, but when tuberculin is injected subcutaneously, or deep into the muscles, there is no pain if the proper technic is followed. I have treated children of all ages, above two years, by the hypodermic method and have never yet had difficulty in using the needle. The first

fear on the part of the child is soon overcome by tact and patience. Injections made directly into the focus of disease have not proved advantageous as yet.

Latham has reported very favorably on the administration of tuberculin by the mouth and has produced opsonic curves, showing that it is operative. With reference to this method, however, I would urge that it leads to too much inexactness to recommend it as a method of value. This inexactness is not only due to the fact that the remedy might be altered by the secretions of the gastrointestinal tract, but also because of the difference in absorptive powers of the mucous membrane of various individuals.

I see no particular advantage in the intravenous method of administration. I personally believe that slowness of absorption is desirable. I cannot believe that anything is gained by throwing the tuberculin directly into the blood-stream. We must remember that Koch used the intravenous route in some of his experimental work and claimed excellent results from it in the increase of antibodies; but it is the clinical condition that must be taken into consideration in our discussion of the method to be employed, and not a laboratory experiment. The very fact that there is some danger in puncturing a vessel and throwing extraneous substances into the blood-stream closes the intravenous method to practitioners in general. If it is to be used, it should be used by specially trained operators under the strictest aseptic precautions and under ideal conditions.

Aside from the desirability of slow absorption and the simplicity of method, the fact that antibodies are probably produced by the cells of the body generally forces me to prefer the subcutaneous route, at least as far as the treatment of pulmonary tuberculosis is concerned. If the injection is made directly into the blood-stream, the tuberculin is carried directly to the lungs, there to come in contact with the cells involved in the infection. In this way the cells which are most directly stimulated are those in the pulmonary tissue. It has also seemed to me that probably one of the reasons why natural healing fails is because these cells near the foci of infection are stimulated to the point where they fail to produce the proper immunizing response. This is more or less theoretical; but, knowing that the other cells of the body will produce antibodies, it seems natural to suppose that the remedy would be more effective if thrown under the

skin, or into the muscles, and allowed to absorb slowly, irritating the healthy cells distant from the focus of infection, and trusting to their producing antibodies necessary for immunity.

On the other hand, it is possible that the pulmonary cells may have some distinct advantage over the other cells of the body in producing antibodies for combating this disease, which seems to have such a predilection for pulmonary tissue; and if so, there would be an advantage in putting the remedy directly into the blood-stream.

I have had no experience in the intravenous administration of tuberculin, but if we are to judge from the experiences of those who have, and those who have not, it would seem that nothing is to be gained by this method.

Method of Diluting Tuberculin.—The same general method of making dilutions is to be carried out for therapeutic use as was mentioned for the subcutaneous tuberculin test. There must be dilutions made so that dosage can be accurately measured. The most common method in this country for making dilutions is to make each dilution ten times weaker than the preceding one. In Europe, Neumann, of Vienna, and Sahli, of Berne, have given methods of dilution very different from this.

One important thing in making up dilutions is to see that they are kept sterile. For this reason it is wise to use a diluting fluid containing some antiseptic. I prefer a normal salt solution, plus .4 per cent of phenol for most of the preparations which I use. Denys, however, prefers that his preparation be diluted with normal salt without any preservative. This can be done, if scrupulous cleanliness be observed. If it is not, however, there is danger of infection and abscess formation.

T.R. may be diluted with normal salt and phenol solution, or a 20 per cent glycerin solution may be used.

Extreme care should be used in making dilutions. The same measuring pipette, or the same syringe, should be used in making up all dilutions, because we take a certain measured quantity of a higher dilution and dilute it a certain number of times for the next dilution. If we should use a different pipette in making one dilution, there might be some alteration in the strength of all the dilutions following; therefore exactness demands that the same instrument be used in making up all dilutions which are to be used in a series.

It is also desirable not to make up too large a quantity at a time. This is the great advantage of a physician's making his own dilutions. I rarely make more than one cubic centimeter of any dilution at a time. Thus, when many patients are under treatment a new dilution is made every day or so. This gives us a fresh dilution at frequent intervals and guarantees, if proper care is exercised, that it will not last long enough to be contaminated. Another advantage of making up small quantities is that the weaker ones lose their strength after a few weeks, and if new dilutions were made and utilized in the treatment of the same patient, reactions might occur unless the dose was reduced. Whenever a preparation becomes cloudy it should be discarded. Making up small quantities of dilutions also prevents waste; and waste becomes very important in the more costly preparations.

Emulsions must always be shaken before dilutions are made from them and before the dose is removed for use.

The following tables will show the method of making dilutions of the more common preparations of tuberculin used in America. I shall also give the value of one cubic centimeter of each dilution both in terms of milligrams according to the old method, and in cubic millimeters, according to the new method, as advocated on page 162. The advantage of this new method will be readily seen by glancing at the tables. I believe that it will be appreciated, although it will be somewhat confusing at first to those who have followed the older method. Its accuracy recommends it.

Some apparent discrepancies will appear in my first two tables. All of the extracellular preparations, O.T., B.F., A.T.O., and P.T.O., were originally measured in terms of milligrams, and while this was an error, it has continued up to the present time. O.T. was taken as the measure as having 1000 milligrams to the cubic centimeter. Inasmuch as B.F., A.T.O., and P.T.O. are not concentrated, when compared with O.T., they contain only one tenth the amount of bacillary toxins, consequently they only contain 100 milligrams to the cubic centimeter. Therefore 1 cubic centimeter of O.T. will appear as having 1000 milligrams and 1000 cubic millimeters, while 1 cubic centimeter of B.F., A.T.O., and P.T.O. will have 100 milligrams and 1000 cubic millimeters.

TABLE I

TABLE SHOWING METHOD OF DILUTING O.T. (KOCH), with value of 1 c.c. of each dilution in both mg. and c.mm.

(Diluent: sterilized normal salt solution + .4 per cent phenol.)

							Solution No.	of which 1 c.c. contains	
								in milligrams	in cubic millimeters
1.	c.c.	original	solution				0	1000.	1000.
.1	c.c.	"	"	+ .9	c.c.	diluent	= I	100.	100.
.1	c.c.	I	"	+ .9	c.c.	"	= II	10.	10.
.1	c.c.	II	"	+ .9	c.c.	"	= III	1.	1.
.1	c.c.	III	"	+ .9	c.c.	"	= IV	.1	.1
.1	c.c.	IV	"	+ .9	c.c.	"	= V	.01	.01
.1	c.c.	V	"	+ .9	c.c.	"	= VI	.001	.001

TABLE II

TABLE SHOWING METHOD OF DILUTING A.T.O. (KOCH), P.T.O. (SPENGLER), AND B.F. (DENYS), with value of 1 c.c. of each dilution in both mg. and c.mm. The discrepancy between the columns in mg. and c.mm. is due to the fact that the mg. column is compared with Koch's old tuberculin, which is ten times stronger than A.T.O., P.T.O., and B.F., in that it is boiled down to one tenth its original volume.

(Diluent: normal salt solution + .4 per cent phenol. Denys prefers normal salt solution alone for B.F.)

							Solution No.	of which 1 c.c. contains	
								milligrams	cubic millimeters
1.	c.c.	original	solution				= 0	100.	1000.
.1	c.c.	0	"	+ .9	c.c.	diluent	= I	10.	100.
.1	c.c.	I	"	+ .9	c.c.	"	= II	1.	10.
.1	c.c.	II	"	+ .9	c.c.	"	= III	.1	1.
.1	c.c.	III	"	+ .9	c.c.	"	= IV	.01	.1
.1	c.c.	IV	"	+ .9	c.c.	"	= V	.001	.01
.1	c.c.	V	"	+ .9	c.c.	"	= VI	.0001	.001

TABLE III

TABLE SHOWING METHOD OF DILUTING T.R. (KOCH) AND WATERY EXTRACT (VON RUCK), with value of 1 c.c. of each dilution in milligrams of bacillary substance and cubic millimeters of original solution.

(Diluent: Normal salt solution + .4 per cent phenol. Koch preferred normal salt solution + 20 per cent glycerin for T.R.)

	Solution No.	of which 1 c.c. contains	
		bacillary substance in milligrams	original solution in cubic millimeters
1. c.c. original solution	= 0	10.	1000.
.1 c.c. " " + .9 c.c. diluent	= I	1.	100.
.1 c.c. I " + .9 c.c. "	= II	.1	10.
.1 c.c. II " + .9 c.c. "	= III	.01	1.
.1 c.c. III " + .9 c.c. "	= IV	.001	.1
.1 c.c. IV " + .9 c.c. "	= V	.0001	.01
.1 c.c. V " + .9 c.c. "	= VI	.00001	.001

TABLE IV

TABLE SHOWING METHOD OF DILUTING B.E. (KOCH) AND P.E. (SPENGLER), with value of 1 c.c. of each dilution in milligrams of bacillary substance and cubic millimeters of original solution.

(Diluent: normal salt solution + .4 per cent phenol.)

	Solution No.	of which 1 c.c. contains	
		bacillary substance in milligrams	original solution in cubic millimeters
1. c.c. original solution	= 0	5.	1000.
.2 c.c. " " + .8 c.c. diluent	= I	1.	200.
.1 c.c. I " + .9 c.c. "	= II	.1	20.
.1 c.c. II " + .9 c.c. "	= III	.01	2.
.1 c.c. III " + .9 c.c. "	= IV	.001	.2
.1 c.c. IV " + .9 c.c. "	= V	.0001	.02
.1 c.c. V " + .9 c.c. "	= VI	.00001	.002

Tuberculin Made from Different Strains of Bacilli and Grown on Different Media Differ.—It is a very important point in technic to remember that different preparations of tuberculin,

supposedly made in the same manner, differ widely. If a preparation from one laboratory is being used in treating a patient, it would be a great error to change to a product from another laboratory or from a different media in the same laboratory, without dropping back in dosage. When a new stock of tuberculin is to be used, always drop back to a smaller dose, and if a change is made in the preparation, it is best to commence at or near the very beginning. The dose can then be quickly increased without loss of much time, until the point of tolerance for the new preparation is found.

Physicians Should Know the Value in Milligrams or Cubic Millimeters of Each Dose.—Some writers on the subject of tuberculin think that the amount of tuberculin in the dose is of no consequence and that it is better to remember the dose, not as so many milligrams or such a fraction of a milligram, or such a portion of the original solution, but as so much of a certain dilution. I cannot agree with this. I believe that it is necessary for every possible safeguard to be thrown around tuberculin, and I look upon the amount of tuberculin as expressed in milligrams, or in terms of the original solution, as a very important safeguard. If he who begins the administration of tuberculin realizes that he is using one thousandth of a milligram, it means much more than a part of a certain dilution. He sees that extreme care must be used because such a small amount of the remedy is active.

I would suggest that biological laboratories always state on the label that 1 cubic centimeter dilution No. —— contains —— milligrams of tuberculin, or, according to the new method endorsed in this book, so many cubic millimeters of the original solution. It sounds very careless to hear a scientific man say that he gives two drops of dilution No. 4 or No. 6. This means nothing to him and does not teach the important lesson necessary to the correct administration of tuberculin, or the necessity of individualization. It savors of routine of the strictest order, and should be avoided whenever possible.

While I recognize that tuberculins are not standardized according to their activity and that different preparations are not to be compared, yet this very fact argues against routine. It is the effect that we desire and not the attainment of a certain dose. Therefore he who administers tuberculin should always

realize that he is giving such and such a part of the maximum dose that the average patient can stand.

Many men are wasting their time and jeopardizing their patients' chances of recovery by administering tuberculin without having the least idea of what an average maximum dose of the preparation which they are using is. I have known of patients' being treated for months on "so many drops" of the 5th and 6th dilutions of O.T., as put up by biological laboratories. This dose is not large enough to produce any appreciable immunizing response and cannot be of much value to the patient except as it prepares him for larger doses, which he never receives. This must be appreciated if we are to put tuberculin on a rational basis. Tuberculin is to be judged; therefore it, instead of water, must be given.

Cubic Millimeter as Unit of Dosage.—Riviere and Morland,[1] in order to simplify dosage and make the quantity of tuberculin employed more intelligible, suggest that we discard the old idea of milligrams in which the doses have always been reckoned, though erroneously in all the extracellular products, and measure it in terms of the original solution of each preparation.

This is quite simple. The maximum dose of each preparation is 1 or 2 cubic centimeters, or 1000 or 2000 cubic millimeters. If one desires to know how much solid extract there is in the various emulsions, it can easily be computed; but it is of no advantage to the average man, over the amount of the original solution, and only serves to confuse. It is of value, however, for him to know that he is administering a certain fraction of the maximum dose, say $\frac{1}{1000}$ or $\frac{1}{100}$ of it. This avoids the objection that attaches to "so many drops of a certain dilution," and yet satisfies the desire for a knowledge of the amount of tuberculin contained in each dose. The table on the following page is adapted from Riviere and Morland's book.

While it would be somewhat confusing for those who have learned the old method of dosage to change, yet I would recommend this as a much simpler method for those who are taking up tuberculin treatment anew. I shall give my schema in terms of both, so that both methods may be understood.

Schemata.—I hope that I have made it clear in this monograph that the best results cannot be obtained by the routine employ-

[1] Tuberculin Treatment, Oxford Press, 1912.

TABLE V

THE CUBIC MILLIMETER AS A UNIT OF VOLUME

Cubic Millimeter. c.mm.	Cubic Centimeter. c.c.	Contained in 1 c.c. of dilution	Equivalent on older system of						
			Old tuberculin. Bovine old tuberculin.	T.O.A. P.T.O. B.F.	T.R. Old basis Koch	T.R. New basis Ruppel	P.E. B.E.	T.B.K.	Watery Extract
1000.	1.	original	1000. mg.	100. mg.	10. mg.	2. mg.	5. mg.		10. mg.
100.	0.1	No. I	100. "	10. "	1. "	1/5 "	1/2 "	TB K_1 1.0	1. "
10.	0.01	No. II	10. "	1. "	1/10 "	1/50 "	1/20 "	TB K_2 1.0	1/10 "
1.	0.001	No. III	1. "	1/10 "	1/100 "	1/500 "	1/200 "	TB K_3 1.0	1/100 "
0.1	0.0001	No. IV	1/10 "	1/100 "	1/1000 "	1/5000 "	1/2000 "	TB K_4 1.0	1/1000 "
.01	0.00001	No. V	1/100 "	1/1000 "	1/10000 "	1/50000 "	1/20000 "	TB K_5 1.0	1/10000 "
.001	0.000001	No. VI	1/1000 "	1/10000 "	1/100000 "	1/500000 "	1/200000 "	TB K_6 1.0	1/100000 "

ment of tuberculin, advancing with definite increase in dosage and at set intervals of time. Regardless of this, I find that it is necessary to give a guide to those who are not accustomed to use these remedies, which they may follow with safety until their experience enables them to vary it.

A very common method of dosage is to begin with a definite small dose and increase as follows: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, etc. Owing to the fact that the increase from 1 to 2, 10 to 20, and so on in such a series, is where reactions most commonly occur, the following modified scale has proved better: 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, etc.; or 1, 1.5, 2, 2.5, 3, 5, 7, 10, 15, 20, etc.

The increase in dosage cannot be considered alone. It must be taken into consideration together with the interval between doses. Believing as I do in the desirability of rapidly increasing at the start, I begin back with what might be called an unnecessarily small dose and then advance quickly with short intervals, thus 1, 10, 100, 500, 1000, 1500, 2000, 5000, 7000, etc.

TABLE VI

SCHEMA FOR O.T. AND A.T.O. (KOCH), P.T.O. (SPENGLER), B.F. (DENYS).

No. days showing interval.	Dosage old method.	Dosage new method.
1	1/1000 mg.	0.001 c.mm.
3	1/100 "	0.01 "
5	1/10 "	0.1 "
7	5/10 "	0.5 "
9	1. "	1. "
11	1 1/2 "	1.5 "
13	2. "	2. "
15	4. "	4. "
18	7. "	7. "
21	10. "	10. "
24	15. "	15. "
27	25. "	25. "
31	40. "	40. "
35	60. "	60. "
39	80. "	80. "
43	100. "	100. "
47	150. "	150. "
52	200. "	200. "
57	300. "	300. "
63	400. "	400. "
69	500. "	500. "
77	600. "	600. "
83	700. "	700. "
90	800. "	800. "
98	900. "	900. "
108	1000. "	1000. "

TABLE VII

SCHEMA FOR T.R. (KOCH) AND WATERY EXTRACT (VON RUCK).

No. days showing interval	Dosage old method.	Dosage new method.
1	1/10,000 mg.	0.01 c.mm.
3	1/1,000 "	0.1 "
5	5/1,000 "	0.5 "
7	1/100 "	1. "
9	2/100 "	2. "
11	5/100 "	5. "
13	8/100 "	8. "
16	1/10 "	10. "
19	1½/10 "	15. "
22	3/10 "	30. "
25	5/10 "	50. "
29	7/10 "	70. "
33	1. "	100. "
38	1 1/2 "	150. "
43	2. "	200. "
48	3. "	300. "
53	4. "	400. "
59	5. "	500. "
66	6. "	600. "
73	7. "	700. "
80	8. "	800. "
87	9. "	900. "
94	10. "	1000. "
104	12. "	1200. "
115	15. "	1500. "
130	18. "	1800. "
145	20. "	2000. "

TABLE VIII

SCHEMA FOR B.E. (KOCH) AND P.E. (SPENGLER).

No. days showing interval	Dosage old method.	Dosage new method.
1	1/10,000 mg.	0.02 c.mm.
3	1/1,000 "	0.2 "
5	2/1,000 "	0.4 "
7	3/1,000 "	0.6 "
9	5/1,000 "	1. "
12	7/1,000 "	1.4 "
15	1/100 "	2. "
18	1½/100 "	3. "
21	2/100 "	4. "
24	3/100 "	6. "
27	5/100 "	10. "
30	7/100 "	14. "
34	1/10 "	20. "
38	1½/10 "	30. "
42	2/10 "	40. "
46	3/10 "	60. "
50	5/10 "	100. "
55	7/10 "	140. "
60	1. "	200. "
65	1 3/10 "	260. "
70	1 5/10 "	300. "
75	2. "	400. "
80	3. "	600. "
86	4. "	800. "
93	5. "	1000. "
101	6. "	1200. "
110	7. "	1400. "
120	8. "	1600. "
132	9. "	1800. "
145	10. "	2000. "

The doses in P.V. and T.B.V. (Spengler) are quite different, and I can see no reason for attempting to make them conform to the new scale. The dosage is simple; the increase is tenfold, as a rule, although it may be changed to fivefold, and at times, in advanced cases, I increase by tenths. For an uncomplicated early case, a fibroid, or an inactive chronic ulcerative case, the following schema may be followed:

TABLE IX

No. of days—showing interval	Dosage in mgs. bacillary extract.
1	1/100,000,000
3	1/10,000,000
6	1/1,000,000
10	1/100,000
15	1/10,000
21	1/1,000
31	1/100

The latter dose may be repeated at intervals of about two weeks.

These rapid increases at the beginning of treatment are usually readily tolerated and seem to rapidly produce the insensitiveness desired to make the succeeding dose tolerated better.

The increases mentioned here are somewhat larger than those at times used, but it will be noted that my increases and my intervals bear something of a definite relation. My conception is that, as the dose increases in size, the toximmunity (decreased hypersensibility) that is produced is greater, is slower in appearing, and lasts longer, as shown in Fig. 28. As this period of decreased hypersensitiveness is the time when the succeeding dose should be given, the interval between doses must, of necessity, be gradually increased. The superiority of this method over the attempt to give doses once or twice a week is self-evident. If the dose is given at the point of greatest toximmunity, or greatest insensitiveness, the danger of reaction is least. If given before this time, or after it, a reaction may still not occur, but the danger of such an occurrence is increased. If the next dose is given before or after the period of decreased hypersensitiveness, it must be smaller than if given during this period.

Attempts have been made to figure out dosage so that each succeeding dose is a definite per cent increase over the preced

ing one. This is entirely unnecessary and fails to make use of one of the things which I believe is valuable: that is, the definite stimulation which follows the larger increases.

This irregular stimulation, now a marked focal reaction and then a gradual subsidence of reaction, followed by a lesser one, and then an occasional marked one again, furnishes the conditions which, according to my ideas, are especially favorable to cure.

In following the above schemata, it is necessary to vary according to the rules laid down in other parts of this book, according to reactions, complications, individual susceptibility, the conditions under which the patient is being treated, and so on. If a reaction occurs, always stop until it passes away, but it is necessary to be careful and not confuse reactions with temperature rises, which are due to the natural course of the disease or intercurrent disturbances, as mentioned in preceding chapters.

It must also be borne in mind that these schemata are given for either early or chronic fibroid, or chronic, inactive, ulcerative tuberculosis. For fever cases the advance should be slower. As no one should undertake to treat a severe case from a printed schema, I deem it best to omit such from the monograph. Experience alone can teach one how to treat the severe forms of the disease.

In administering tuberculin, as stated above, the success or failure in therapy depends on little things.

Syringe.—A syringe that can be readily cleansed should be used: the Luer, all-glass, or, what I prefer, the Record with glass barrel and metal piston, is ideal for the purpose (Fig. 25). A syringe graduated to the metric system is preferable because dosage is given in terms of this scale. It should be seen that a syringe is chosen which is divided accurately. If the barrel is of small caliber, making the space between divisions wide, the percentage of error in dosage will be greatly reduced.

When the required dosage is drawn up into the syringe, the piston should be fixed, either by the finger or some other method, so that it does not slip down and force part of the liquid out before the injection is made. I always fix the piston with the first finger of my right hand, and from the time I draw up the dose until the needle is through the skin I never take my finger

from the piston of the syringe. (I hold the syringe as shown in Fig. 26.) The value of this little trick in making for accurate dosage can readily be seen. I always keep a bottle of diluting

Fig. 25.—Record (above) and Luer (below) syringes. Two excellent syringes for the administration of tuberculin. Aseptic and easily sterilized.

fluid for cleansing my syringe. After I have given a dose, I force the piston down several times, forcing out as much of the tuberculin left in the syringe as possible. I then draw the

A B

Fig. 26.—A, Illustrating method of fixing piston of syringe with first finger so as to prevent the tuberculin from escaping from needle, thus helping to insure accuracy in dosage; B, Illustrating method of forcing piston down with the first finger after the needle is inserted into the skin. The finger should not be removed from the position shown in 26 A from the time that the dose is drawn into the syringe until the needle has been inserted under the skin.

syringe full of diluting fluid several times, the number varying according to the dilution used, and force this out through the needle. After filling and emptying the syringe two or three times

in this way, the syringe is free from remains of tuberculin from the preceding dose and can be used again for treating the next patient.

The importance of thoroughly washing the syringe can readily be seen if several patients are being treated at the same time. Suppose one patient is receiving a dilution a million times stronger than the one following. If the syringe is not washed out very thoroughly, instead of the second patient receiving a measured dose one million times smaller, he will receive a dose one million times smaller, plus the remains of the preceding dose, which remained in the syringe. I have known reactions to be produced through carelessness in observing this little point of detail.

Not the least important in the administration of tuberculin is the care of the needle. The best needle for the administration of tuberculin is the platino-iridium needle. This can be brought to a white heat after each injection, and in this way cleanliness is insured. Steel needles may also be used, but where they are used, extra care must be taken in keeping them sterile. Where many patients are being treated in a short space of time, as occurs in dispensaries, if steel needles are used, quite a supply of them should be kept on hand. They should be kept in some antiseptic fluid up to the time they are used. Before I began the use of the platino-iridium needles, I used steel needles, keeping them in alcohol. The needles are boiled and then kept in alcohol until they are used. After the needle is used it is cleansed, dried, and then immersed in alcohol before being used again.

Very important also is the needle point. While any kind of a needle can be used in giving tuberculin, a sharp one is greatly appreciated by the patient. A medium fine emery stone can be used for sharpening either the platino-iridium or steel needle. The needle should be held at the angle desired and rubbed back and forth on the stone carefully without much pressure. The best point is obtained by holding the needle at an angle with the stone, which is not too sharp, as the slant of the needle should not be too long. With a little care in keeping the needle sharp, the injections can be made entirely painlessly, especially if the needle be inserted and withdrawn quickly.

Time of Day of Injection.—The time of day for the injection

does not make very much difference. Some prefer the morning, some prefer the afternoon, and some the evening. Any time will do if the proper allowance is made. Those who give their dose in the evening prefer it because the patient will go to bed and rest during the hours that the reaction might come on, probably saving themselves reactions, which, at times, might be induced by exertion following the dose. Those who prefer giving it in the morning do so because if a reaction does occur it is more apt to be observed than where the dose is given in the afternoon or at night.

The time of reaction, however, differs considerably, according to the preparation used. A reaction from human tuberculin is

Fig. 27.—Tuberculin tray.

more apt to come on early than that from the bovine. The bovine usually comes the second day if the dose is given in the morning, while the human usually shows itself the first day. I do not think that the time of day is of sufficient importance to cause the physician or patient to put themselves out in order to make the injection at a certain time. It is largely a matter of convenience.

Tuberculin Tray.—In an institution it is necessary to have some convenient way for carrying tuberculin and vaccine to those who must be treated in bed. Fig. 27 shows a tray which has been in use at the Pottenger Sanatorium for Diseases of the

Lungs and Throat for several years, and which has proved very satisfactory. Besides carrying a full set of dilutions of two or more different tuberculins, there is room for bottles of special vaccines, old tuberculin for the tuberculin tests, an alcohol lamp for sterilizing the needle, several bottles of diluting fluid for washing out the syringe, a jar containing pledgets of cotton, and a beeker containing alcohol for use in disinfecting the skin, and racks carrying two hypodermic needles, one for the administration of tuberculin and the other for administrations of iron, arsenic, and strychnia and other such remedies.

The tray is simple of construction, consisting of two sheets of metal separated about one inch, the bottom one being solid, the upper one containing holes for the bottles. The two are fastened together by the four metal posts, which are united to make the handle, and a sufficient number of separate posts placed here and there between the metal sheets to make the tray solid. Any metal worker with a little ingenuity can make such a tray. I recommend it as being a great convenience.

How to Avoid Errors in Dosage.—In order to avoid errors in dosage, it is necessary for the physician to fix the dose thoroughly in his mind and hold his attention on it until it is administered. Aside from having exact dilutions and a syringe that is accurate in measurements, the physician must use every precaution to guarantee that he gives the dose intended. My method is as follows:

I first determine the dose which is to be given. I write this dose down on the patient's chart. I then write it down in my own record book. I then draw the dose up into the syringe and again look at the dose on the chart, which I always keep lying before me until the dose is administered, and then compare it with the label on the bottle before administering it. Thus, by keeping the dose constantly before my eyes, it is thoroughly fixed in my mind, and by comparing it with the label on the bottle before the dose is given, danger of error is practically eliminated. It takes no more time to measure the dose this way than it does to do it carelessly. The processes are reduced to a system, so that they are done in an instant. One other precaution should be used: the physician should not talk or allow his attention to be withdrawn from what he is doing until the dose has been measured and administered.

Site of Injection.—The site of injection is also of little moment. Tuberculin can be given on any portion of the surface of the body. I prefer the flexor surface of the forearm, simply because it is convenient for both physician and patient. I prefer always to put the tuberculin in the subcutaneous tissues, at about the same depth, for by so doing I can observe the effect of reactions better. A local reaction at the point of injection should always be given due consideration. It is an index of the sensitiveness of the patient and when it is present indicates that caution must be used in order to avoid general reactions.

Carl Spengler has long taught that a reaction at the point of injection is coextensive in point of time with the focal reaction. Whether this is true or not, it is best, in administering tuberculin, to wait until all local reaction has disappeared before giving the next dose. The site of injection should be changed. It is not best to use the same place constantly. I change from one arm to the other and aim to give each successive dose in a new location.

Local Reactions Where Previous Inoculations Have Been Given.—The fact that a local reaction often occurs in the eye where the conjunctival test has been previously given, or at the point of inoculation where the von Pirquet has been given when the patient is put on therapeutic doses of tuberculin, or at the point of a subcutaneous injection when a succeeding injection is given, requires some explanation. It seems to me that the same explanation will apply to all of these conditions: namely, that when the tuberculin is brought in contact with the cells, either by applying it to the conjunctiva, or to the subcutaneous lymph-cells by the skin test, or in the subcutaneous tissues when given therapeutically, the local cells are stimulated to the production of antibodies, some of which are probably thrown off to circulate in the blood-stream, while others remain anchored to the cells which produce them. When a subcutaneous injection of tuberculin is given later, if the dose be sufficiently large to produce an excess over the amount necessary to combine with the free receptors found in the blood-stream, the excess will continue circulating in the form of toxin until it meets these receptors, which have been formed by and remained attached to the various local cells where the tuberculin has been applied. I look upon these reactions as

having the same explanation as the reaction which occurs in the focus of infection.

That this explanation is probably correct is also indicated by the fact that injections of tuberculin produce histological tubercles, the same as injections of tubercle bacilli, as has been shown by numerous observers. This explanation also shows why these local reactions should be considered as being coextensive in point of time with the reaction in the tuberculous focus.

Initial Dose and Method of Increasing.—There seems to be a great deal of confusion and misunderstanding regarding the initial dose of tuberculin, also the method of advancing after the initial dose has been given. It does not make much difference what the initial dose is, providing that it is sufficiently small to be sure that it does not produce a reaction, but the succeeding doses must be regulated accordingly. In my own practice I make my initial dose very small, so small that I can increase rapidly; as shown in Table VI, page 164. If we have in view the establishment of a toximmunity, it is important to make a decided impression on the patient in the first few doses that we administer. While we do not desire to destroy the hypersensitiveness of the patient, yet we desire to bring it under control, so that we can manage it at will. This is best accomplished by first producing a marked insensitiveness. If our method is that followed by Wright, we must take an entirely different course, because toximmunity is not aimed at. I have used both of these methods of treatment, but prefer the production of toximmunity, believing that it is equally valuable in localized lesions and far more efficacious in lesions which are more widely spread. In the production of toximmunity, my method differs slightly from that described by others, in that I am bolder in the increase of my early doses and often in my later also. I begin with very small doses; then, after a short interval, I increase rapidly. For the first few doses, I usually increase by two, five, or ten times the preceding dose, according to the preparation used and the lesion to be treated, increasing more slowly where the extracellular toxins are used, and also when the disease is active, whether early or advanced.

I recognize the fact that this conflicts somewhat with the usual idea, but I believe that it is correct; at least, I have found this

method best in my own practice. I believe that the method of rapid increase is the one that will produce the greatest degree of toximmunity and render the patient the most easy of control as far as the administration of the remedy is concerned; therefore, I would suggest, instead of increasing so gradually, as is usually recommended at the beginning of treatment, that we start with a very small dose, making the second dose two, five, or ten times the first, the third dose two, five, or ten times the second, and so on until four or five doses are given. Then, after we have arrived at a fair-sized dose, we can go more slowly, at least more slowly than that indicated by the ten-times method of increase.

This method differs essentially from that employed by Sahli. Sahli greatly fears the effect of reactions and has devised such a carefully increased scheme of dosage that each succeeding dose is a very small increase over the preceding one, believing that this insures the greatest safety from reactions. I am sure, however, that it cannot be any more free from reaction than the method I employ; and I also believe that the plan of rapid increase in doses gives us a distinct advantage in those cases where a marked focal stimulation is desired. With Sahli's method a long time is required to arrive at a dose of considerable size; and there is such a gradual addition of the toxin that the method fails to produce any great change over the gradual dosage of toxins as given out from the focus of infection. The marked stimulation which comes from a large increase of doses of toxin, and which seems to be so valuable in hastening healing, is entirely lacking.

The method which I employ produces the same toximmunity as does the other, but it produces it by a large increase in dosage, thus making a profound impression upon the machinery of immunization and calling forth a generous response in antibodies, and at the same time producing a well-marked focal reaction. When this method is followed, the patient is enabled to stand repeated large increases without reaction. It gives the physician good control of the patient's immunizing response. In my own practice I rarely have a temperature reaction; even the slightest rise in the temperature curve being very infrequent, while focal reactions are well controlled.

By either of these methods tuberculin may be administered with almost perfect comfort as far as the patient is concerned.

the only discomfort being a slightly painful induration occasionally at the point of injection.

Experience in the use of tuberculin is all important for obtaining best results. After one becomes conversant with the remedy he can do things that he cannot do when he is beginning the employment of it. I would not recommend the large increase of dosage which I employ myself for a beginner, especially one who is taking it up alone. I would suggest that he use a less rapid increase, but that he increase faster than the method which is usually given. I think each successive dose should be a marked increase over the last, unless a reaction occurs; and while we are employing small doses at the beginning, each successive dose should not be less than twice as large as the preceding. As we proceed the advance in dosage should be relatively smaller, but always a substantial increase over the preceding one.

In the old method of dosage which was so long in vogue, where each dilution was ten times the preceding, and the doses were increased by tenths, until a syringeful of dilution was given, and then the dose increased again by tenths of the stronger dilution, there was always danger of a reaction occurring between the one-tenth and two-tenth doses, because the dose was doubled when the patient was accustomed to only a one-tenth increase. The method which I use consists of an increase of two, five, or ten times the preceding dose during the small doses, and a very substantial increase as the dose becomes larger. My method gives a large but continuous increase; while the old one gave a small one for a time, then a large one, then a small one for a time again, followed by another large one, and so on. I have noticed that, if we are ascending by a small increase, it is more hazardous to give a large increase than if we have gradually ascended by large increases; for example, if I am making each dose twice the preceding, I find that, if I jump to five or ten times the preceding, there is danger of a reaction, while if I have been increasing by five or ten times the preceding, a reaction does not occur.

Interval Between Dosage.—Not only is the size of the initial dose and the successive doses important, but the interval is of the greatest importance. There is a time immediately following each dose of tuberculin when, if another dose were given, a reaction would most probably occur. Immediately following this, a de-

crease in hypersensitiveness, or an increased tolerance of the patient toward tuberculin, is manifested. This period represents the time when the increased immunity response is evident, and is characterized by an increased number of free receptors circulating in the body fluids, ready to combine with larger quantities of toxins if they should be introduced into the body, either from a tuberculous focus or by artificial administration. When this disappears we have again a period of increased hypersensitiveness and increased liability to reaction. The length of the period of heightened immunity or decreased hypersensitiveness varies according to the patient's reactive powers and according to the size of the dose, coming on quicker and passing off quicker following a small dose than a large one. It is during this period of increased tolerance that the next dose should be given. The increased danger of reaction immediately following a dose is easy to understand because there is a limit of tolerance; and if a larger dose than this limit be given, a reaction will occur, whether it all be given at once or whether it be divided and the second administered before the first dose is properly cared for. This is what would happen if the second dose was given immediately on the heels of the preceding one or at any time before the period of increased immunity, or decreased hypersensitiveness had arrived. The increased immunity following each dose lasts only for a certain length of time; then, if another large dose is given, after this period of increased tolerance has passed away—that is, after the increase of antibodies produced by the preceding dose has partly disappeared from the circulation—the dose will be too large to be rendered innocuous by the antibodies present, and the surplus of toxin will produce a reaction.

My meaning can be grasped better by referring to Fig. 28, which shows schematically my conception of what occurs after a dose of tuberculin. When a dose is given, it will be seen that the same general phenomena occur, whether the dose be small, medium, large, or very large, but that there is a wide variation in the various phases of reaction marked by the line *x*, *a*, *b*, *c*. The depression in the curve marked *a* follows each dose. This corresponds to the period of incubation in infectious diseases and represents the time when the free receptors are combining with the tuberculin. There is a temporary decrease of the free receptors on this account. We assume that the

of receptors, both free and anchored, increase a certain amount after each injection according to the quantity of tubercle protein injected. Therefore, as the dose is gradually increased, more free receptors are formed in the blood-stream, and an increased tolerance to tuberculin is established. This is represented by that part of the curve marked *B*. If a second dose be given during that part of the curve marked *a*, it is practically the same in effect as adding its amount to the amount of the dose

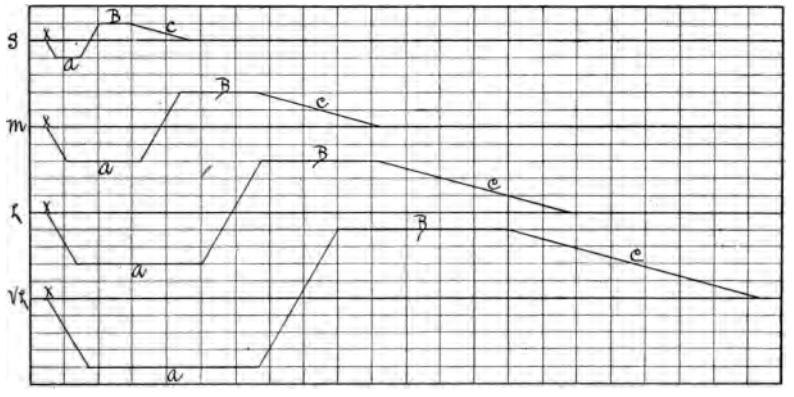


Fig. 28.—Illustrating schematically the phenomena that follow a dose of tuberculin, and showing when to give and when not to give the dose. "x" represents the time when the dose is given. The letters "s" meaning small, "m," medium, "l," large, and "vl," very large, indicate the size of the dose. That part of the line marked "a" represents the period when the antibodies are reduced because of caring for the dose. It is marked by an increased hypersensitiveness and decreased tolerance of tuberculin. If another dose is given at *this* time, it is equal to increasing the dose "x" by the amount given, and if large enough, causes a reaction. "B" represents the time when the body has reacted in the production of an increased number of antibodies; therefore it is marked by decreased hypersensitiveness and an increased tolerance of tuberculin. During this time an increase in dosage is readily tolerated. "c" represents the time when the increased amount of antibodies resulting from the previous dose is gradually disappearing. This period is characterized by a gradual increase in hypersensibility and a gradually reduced tolerance to tuberculin. If a dose is given during this time, it is likely to cause a reaction, especially if the amount of tuberculin be increased. It will be noticed that the same phenomena follow doses regardless of size, but that the various phases are larger, the larger the dose, showing that the interval between doses must increase with the size of the dose.

given at *x*, and if the two combined are greater than the free receptors are able to satisfy, a reaction will occur. If the succeeding dose be given during that portion of the curve marked *B*, however, a considerable increase of toxin will be borne without reaction occurring, because this is the period when the body is protected by an increased quantity of receptors. In the method of using tuberculin so as to produce a high grade of toximmunity without reaction, the increased dose should be given in that part

of the curve marked *B*. After the tubercle protein has been injected and it has called forth the immunizing response represented by the increase in receptors shown by that part of the curve marked *B*, an adjustment takes place. The receptors, not being required for further defense, begin to disappear as shown by a fall in the curve marked *c*. If another increase in tubercle protein should be injected during that time represented by that part of the curve marked *c*, a reaction would most likely occur, because the total quantity of specific receptors has again decreased.

The principles just mentioned must be taken into account in spacing our doses. It is safe to give small doses with intervals of one or two days; but when the larger doses have been reached, an interval of ten days or two weeks should elapse. My experience has taught me also that the period of maximum immunity or the period of least danger for a succeeding dose is not a very long one. The time when a dose should be administered cannot be shortened or lengthened at will. I think in failing to grasp the importance of this period of increased tolerance is where many fail when they try to give tuberculin according to rule. I do not believe that it is possible to administer tuberculin to the greatest advantage of the patient and to the production of the greatest toximmunity, and still control the focal reactions, by giving it twice a week, or once a week, or every ten days, according to rule. I recognize that a certain routine is essential to those who do not have sufficient experience to form a judgment as to when the doses should be given; but for those who have, I feel that they are not doing their patients the most good by adopting a routine method.

We can now understand and harmonize the two methods of administering tuberculin, the one aiming by small infrequent doses to keep up the hypersensitiveness of the patient, the other aiming, by continually increasing the amount of tuberculin given, to produce a high grade of toximmunity or decreased hypersensitiveness. The small dose given infrequently is followed by repeated individual reactions, as shown in Fig. 29 (1). The increase in receptors is practically allowed to come and go before the succeeding dose is given. Therefore each dose represents an independent immunizing and healing response. The plan of producing a high grade of toximmunity, on the other hand, implies

taking advantage of the response called forth by a preceding injection, so that each succeeding dose may be markedly increased without exhausting the increased numbers of receptors. This method supposes the succeeding dose, if increased, to be always given during the time indicated by the letter *B* in the curve, as shown in Fig. 29 (2). If the dose is given during the *B* portion of the curve, it may be increased within reasonable limits, such as are represented by the schema which I have given without fear of reaction. When a final large dose has been reached it may be

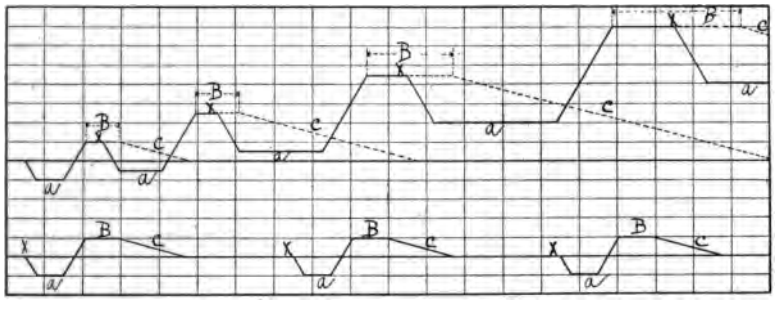


Fig. 29.—Schematic representation of the phenomena that occur (1) in the repeated use of small doses, (2) in the production of toximmunity. It will be noticed that in the use of repeated small doses the phenomena occur after the dose is allowed to disappear entirely, and that each dose stands out as an individual injection. In the production of toximmunity, however, each succeeding dose is given in the "B" portion of the line, and instead of the line gradually dropping back to the normal as it does in the individual dose, illustrated by the dotted line "c," it takes a drop to "a," and then rises above the line of the previous level, and thus builds up a decreased hypersensibility or an increased toximmunity.

repeated and still call forth a reactive response by giving it during the *c* portion of the curve.

This conception also shows why tuberculin cannot be given by rule to best advantage if toximmunity is to be arrived at. The larger the dose the more marked the response and the greater the deviation in the various portions of the curve. If reactions are to be avoided, the interval between the doses must be increased as the dose increases; otherwise the succeeding dose will be falling on the *a* portion of the curve and producing reactions. It can readily be seen from the diagram that it is impossible to build up any considerable toximmunity by giving doses so far apart that they fall on the *c* portion of the curve.

The method aiming at the production of toximmunity is more difficult to employ than the one consisting of repeated small doses, but after considerable experience in both, I prefer it, be

cause I am able to produce better results with it. Theoretically, the immune content of the blood is higher, and the focal reaction is utilized to a greater extent where toximmunity is aimed at.

I treat many ambulatory cases among those of very small means, who are compelled to carry on their work during treatment, and consequently cannot visit me oftener than once or twice a week. This makes it necessary to employ certain definite intervals between doses. I find that I can suit the dose to these intervals, but not to the same advantage that I can when I see the patient oftener. In the sanatorium, on the other hand, where I see my patients daily, I give a dose without reference to the particular interval of time, but according to the patient's condition and the size and action of the preceding dose. I find that I can control my focal reactions better and produce better and quicker results under the latter condition than under the former. *Individualization in size of dose, in method of increase, and interval between dosage is absolutely essential to best results.* Where one, however, does not have the experience on which to base judgment, he can obtain results and do his patients great good by following some routine scheme of dosage, such as is laid down in this and other books similar to it; but as soon as one is able to do so, I would urge him to individualize rather than follow a routine. This point is common sense, but it is too frequently neglected in therapy.

Maximum Dose.—From what I have said regarding individualization throughout this monograph, my idea of a final dose is evident. There is no final dose of tuberculin for all patients. It is purely a matter of individualization. It should not be our aim to reach a definite dose, but to produce definite results. In one patient this can be produced with a much smaller dose than in another. Patients naturally show great differences in the way they are affected by the toxins of tuberculosis, so do we find that they differ in their response to the administration of tuberculin. I make my final dose the one which produces, to my mind, the maximum effect in a given case, and the one beyond which I feel that it is not safe to go without harm; or the one which I feel has produced the highest action that it is possible to produce. I cannot be more definite than this in my writing, because I consider each patient as an individual, and meet the conditions as they arise. This is the point where everyone who attempts to

tell how to do a thing fails; yet it is the information which is most desired.

The dose which is usually given as the maximum dose does not need to be attained in every case, but it should be considered the maximum dose that can be tolerated safely by most patients who are suffering from early, chronic fibroid or chronic, inactive, ulcerative tuberculosis.

There are certain conditions which we meet in clinical tuberculosis which I feel are best influenced by a short temporary stimulation. There are others which I feel improve faster by a prolonged stimulation. When I treat extensive active lesions I employ much smaller doses with less rapid increase than in early and inactive cases. I usually run up in my dosage, then drop back and run up again; while in early cases I am apt to begin with small doses, run up very rapidly, then, after I reach a moderately high dose, increase less rapidly and carry the stimulation of the large dose over a prolonged period of time. In the large doses the focal stimulation may be increased by giving the dose when the period of increased immunity to the toxins is passing away. This same method I also carry out in chronic fibroid tuberculosis, with no, or little, ulceration, and in some cases of chronic ulcerative tuberculosis which have approached the period of healing, but I almost never use this method in chronic active cases.

Duration of Treatment.—There are many methods employed in treating tuberculosis, but any method, to be successful, must take into consideration the production of a state of high efficiency of the body cells and the utilization of tuberculin either by autoinoculation or by artificial administration; and as I said in another part of this book, the duration of tuberculin treatment is coextensive with the duration of any other method of treatment that is carried out. I think this can be readily understood if one fully comprehends what tuberculin treatment is. I do not mean by this that it is always necessary to keep a patient under constant treatment during several years of illness. It sometimes seems best to use Petruschky's method, advancing rapidly to a high dose, and then letting the patient rest for a period of two or three months, allowing the high degree of insensitiveness which has been developed to pass away, and then advancing again; but no matter what method is followed, tuberculin treatment should

be carried out until the best possible result has been attained, whether this be six months or several years.

Some very good men are in the habit of saying that it is useless to begin tuberculin treatment unless the patient can remain under treatment for six months or a year. I am positive that I have seen good results from a single dose of tuberculin. I refer here to the dose which produced a reaction when given for diagnostic purposes. I should put a patient on treatment if I could only treat him for a month, and I feel sure that in many cases that I have so treated I have seen good results follow. I have been able in numerous instances in this way to start patients on the road to recovery, when they had not been progressing favorably previously. I should not break off treatment at the end of so short a period from choice. The point I wish to make, however, is that there is no definite time that must be spent in treatment. Tuberculin treatment for a month will do some good, the same as open-air treatment for a month will do some good. It is not necessary to withhold it simply because a patient cannot be under treatment for six months or a year.

After-Course of Tuberculin.—Remembering that tuberculosis is not healed in six months or a year, even though all symptoms have disappeared, and the patient has returned to his normal physical condition, it is my advice to patients, no matter how good a result has been obtained, that the injections of tuberculin should be repeated at intervals after the first treatment has ended. I usually advise the use of tuberculin for a short period, after the lapse of six or nine months from the time the first treatment has ended, and then again six or nine months after the second treatment has ended. In these after-treatments I advance the dose rapidly, only requiring six weeks or two months to reach the dose which I consider as the maximum for the patient. It is surprising to see how many patients after taking these after-series of injections will experience an increase in general nutrition, an improvement in general symptoms, and an increased feeling of well-being which they had not felt before, since their illness began. I consider that these after-treatments render the result more permanent. They furnish both the stimulation to the machinery of immunization necessary to raise the content of antibodies in the tissues and the focal stimulation which is necessary to complete the healing of the tuberculous

process. We are endeavoring to cure tuberculosis as rapidly as possible, but we find that, no matter how rapidly we go, it is still a long-drawn-out process and we must not shorten it at the expense of a good result.

When to Avoid Focal Reaction.—I believe that the focal reaction is the main feature in healing tuberculosis. While it is desirable and essential to keep the immune content of the blood high in order to prevent the disease extending, yet it is the focal reaction which brings about the healing of the infection that is already present. The focal reaction, however, should be within control. We should know our patient and understand the nature of his tuberculous process. We should produce focal reactions sufficiently strong to facilitate healing, but not sufficiently marked to hasten necrosis and destruction of tissue. Focal reactions should especially be kept under control in acute cases, or where extensive active symptoms are present. Therefore, it is necessary, not only to watch the temperature curve, but to watch other symptoms which are indicative of focal stimulation; for example, when the lung is involved, any increase in cough or expectoration, or feeling of constriction in the chest, or any tinge of blood in the sputum that can be attributed to focal stimulation, should be watched for and taken into account in our dosage. So should symptoms of focal reaction in any other organ be heeded. Also the feeling of malaise or increased nervousness that usually precedes a marked stimulation should be carefully observed.

When to Produce Focal Reaction.—In treating early cases where the disease is not very extensive and the symptoms are not pronounced, also in chronic fibroid tuberculosis and chronic inactive ulcerative tuberculosis which is not extensive, focal reactions may be produced and maintained over a prolonged period of time to the decided benefit of the patient. Under such circumstances one focal reaction must be allowed to pass off before the next one is produced. I have seen old sluggish cavities take upon themselves a decided turn toward healing following a marked focal reaction. I have seen chronic fibroid tuberculosis make much better progress when a marked focal reaction was repeated time after time. It will be recalled, as I mentioned before, that a focal reaction can be maintained short of a temperature reaction. We very often find patients with slight or chronic quiescent lesions, running a daily temperature of about 99° or

99½°, which proves very obstinate. I have found that the best way to treat such cases is by making a distinct impression upon them by producing a marked focal reaction; and now and then, where the patient has run on for months with this kind of a temperature, I have been able by rapid increase of dosage to bring the temperature to normal, the change usually occurring coincident with a large dose of tuberculin. Unfortunately, however, this cannot always be done so easily. These temperatures are sometimes extremely stubborn.

Necessity of Controlling Doses by the Extent of the Focal Reaction.—It is always wise to make use of the focal reactions where possible in controlling both the size of the doses and the interval between doses in administering tuberculin. For example, if there is a visible tuberculous process, such as is often found in the larynx, or occasionally in the pharynx, the action of tuberculin on these local processes can be used to great advantage for control. If the superficial glands are enlarged we can sometimes see an increased inflammation in them following the dose.

In cases of pulmonary tuberculosis any increase of cough or expectoration following a dose should be noted. Especially, however, is it valuable to watch the focal reaction when the dosage has become quite large. It is advisable in such cases to examine the patient's chest after each large dose. I very often examine for five or six consecutive days following these large doses, noting the amount of the focal reaction and the length of its duration. This gives very important information as to the advisability of increasing the dose or of going somewhat more slowly.

Importance of Minute Records of Chest Examinations for Comparison.—In order to be able to do most for those under treatment for tuberculosis, and especially those under tuberculin treatment, the patient should be examined at regular intervals, and accurate charts of the chest should be made for comparison. These charts should be sufficiently minute to give the examiner an intelligent idea of the process and the changes which have taken place from time to time.

Not only do these charts serve a scientific purpose for the examiner, but if properly utilized, may be a tremendous factor in encouraging the patient when the disease is healing satisfactorily. They may also be utilized to advantage in proving to

him the necessity of greater caution and patience when retrograde changes are occurring. How much to tell the patient is a difficult question to decide. It depends a great deal on the patient, but a great deal more on the physician. I, personally, pursue a very frank policy with my patients. I take them into my confidence and explain from the charts made on physical examination what is occurring and what may be expected to occur. This makes the patient more intelligent, and for me, at least, secures a greater co-operation. It takes time, and it presupposes a close association of patient and physician.

In recording my findings I have discarded all attempts to use symbols and follow the plan taught me by Dr. Karl von Ruck, which consists in describing the sounds heard with the stethoscope, just as nearly as I can. The chart is blocked out in squares, each one of which represents an intercostal space. Three records are made in each intercostal space, anteriorly and posteriorly. While this method has the disadvantage of taking a great deal of time, it pays because of its exactness when compared with the usual methods. The charts shown in Figs. 30 A and B show such charts made out according to the physical examination of a patient made on entering the sanatorium, and ten months later. The improvement is plainly visible to a layman.

Examinations for comparison should not be made too frequently, because the changes come slowly, and there is not sufficient difference to be noted; yet they should not be so far apart as to cause neglect of the patient. The physician should always know the condition of his patient's chest. Too frequent examinations, on the other hand, are harmful. They serve no comparative purpose. They keep the patient unduly anxious and cause the patient to expect changes faster than they can possibly occur. I consider once a month often enough for a careful chest examination, unless intercurrent troubles come on, or some symptom calls for an examination at the time.

Value of the Graphic Temperature Chart.—While the graphic chart is not indispensable in the treatment of tuberculosis, yet it is almost so. It is necessary to carry in mind a comprehensive idea of the patient's temperature and pulse, especially since these indicate the various changes occurring in the lung, as well as the little complications that come in. It is impossible for any one to have this comprehensive idea when the temperature is

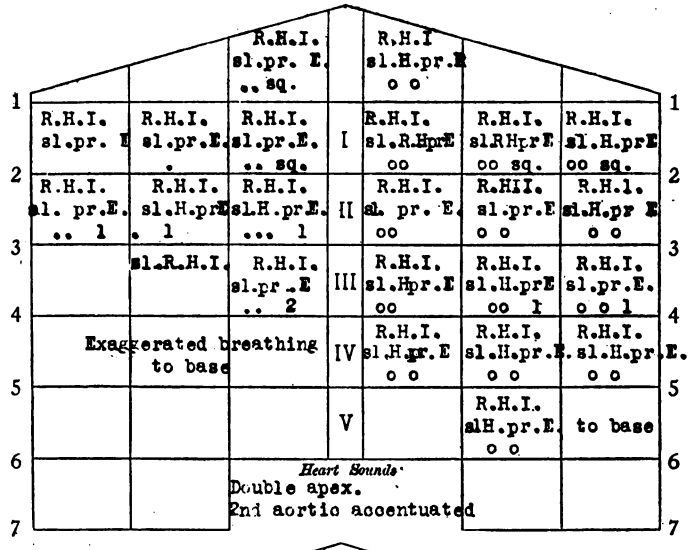


Fig. 30 A

Fig. 30.—A and B. Illustrating method of recording ausculatory phenomena. Instead of using signs, the various sounds as heard are recorded in each space. Fig. 30 B was made ten months after Fig. 30 A, and shows the improvement in the various areas. At this time the patient has fully regained his physical condition, has had an absence of all symptoms for three months; no expectoration.

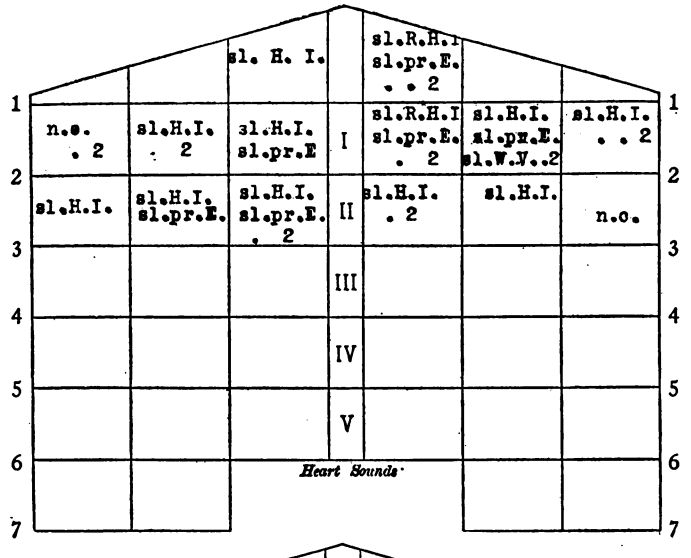


Fig. 30 B

E.	Expiration
H.	Harsh
I.	Inspiration
nc.	Nearly clear
pr.	Prolonged
R.	Rough
sl.	Slight
sq.	Squeaking
W.V.	Whispering voice
...	Fine dry rales
ooo	Medium moist rales
1	On deep breathing
2	On coughing

simply recorded four times a day in a small book, or on a blank chart kept for the purpose, but if the curve is made daily, we have a record that gives us the information that we desire at a glance. These graphic charts also prevent many mistakes in giving tuberculin. The charts which I use are so arranged as to record four daily observations for an entire month. I always have the patient keep at least two of these charts with him, and where the case is at all serious, I keep all the charts together for daily, ready inspection. (My chart is shown on page 207.)

The little record book of symptoms devised by Brown has many advantages. It has a special influence in keeping the pa-

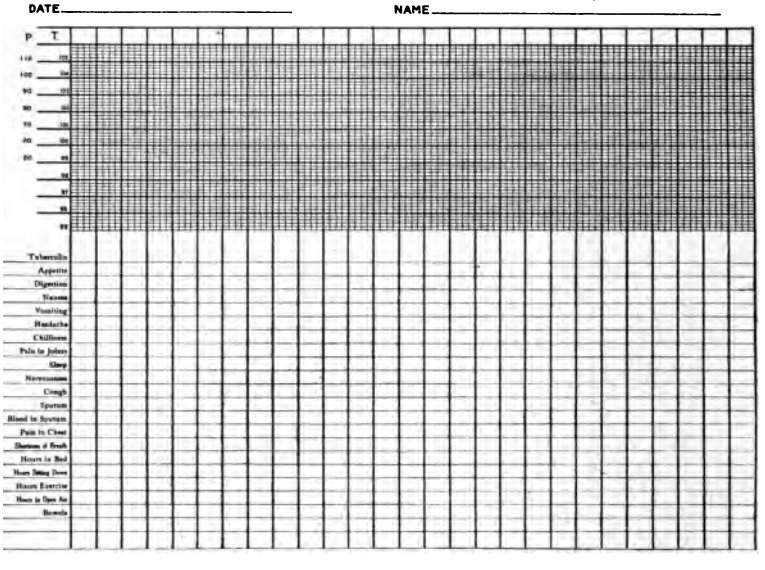


Fig. 31.—Illustrating a convenient graphic chart for temperature and pulse, with record of symptoms added. This is used by Dr. George H. Evans of San Francisco.

tient interested and teaching him the importance of these little things; but what I think is even better than this, is a combination of this with the temperature chart. (Fig. 31 represents such a chart used by George H. Evans.) It is necessary in the administration of tuberculin, as I have said elsewhere, to use every precaution to prevent error, and the advantage of such a chart as this as a guide can at once be seen, the disadvantage being that it makes the patient introspective.

How Are We to Judge the Value of Tuberculin.—It is usually

said that if tuberculin is producing the proper result the patient experiences a feeling of well-being, his symptoms disappear, his cough becomes less, his sputum decreases, he becomes less nervous, sleeps better, and so on. This is true, and it is not true. It depends entirely on the case. A patient may be doing as well as it is possible for him to do, and yet he may experience no feelings of well-being and no decrease of cough and expectoration; on the contrary, it may increase, he may be more nervous and not feel so well, and yet the tuberculin have nothing whatever to do with the apparent changes for the worse. It must be distinctly understood that in active tuberculosis tuberculin cannot stop the symptoms at once, and yet it may do the patient good.

In early tuberculosis, where the disease is not so extensive and the patient's general constitution has not been seriously disturbed, also in chronic fibroid tuberculosis, and in chronic inactive ulcerative tuberculosis, there is nearly always an improvement as soon as the administration of tuberculin has been started. In extensive active tuberculosis, however, this is less often true. It must be remembered that any active case of tuberculosis is liable to take on increased symptoms at any time. This type of disease runs a very uneven course, the patient feeling now better and then worse. When a diseased focus in the lung begins to inflame and break down, it is accompanied by symptoms of increased cough and expectoration, lessened appetite, indigestion, increased nervousness, and sometimes aching and insomnia. These symptoms are not due to tuberculin; and tuberculin may be doing this patient good and yet not be able to stop these symptoms immediately, or even at all. If the use of the remedy is persisted in, however, and all other methods that we know are adopted at the same time, we shall give this patient his best chance of cure and shall sometimes be able to see these untoward symptoms become less and less and the patient improve in the general way that is so often described in books. His appetite will return; he will sleep better; he will be less nervous; his cough will decrease; he will probably put on weight and experience an improvement in his general condition. His sputum, on the other hand, may increase, because with many of these periods there is an increased destruction of tissue with cavity formation and expulsion of tuberculous material

tion of the remedy. Every patient who has tuberculosis treats himself with tuberculin, and it would seem strange to me if there were cases that could not be so treated artificially. It would seem strange if there should be individuals afflicted with a certain disease who were so constituted that they could not tolerate the remedy necessary for cure. I believe that tuberculin therapy can be adapted to any patient and that increased experience and a better understanding of the remedy will show this to be a fact.

When to Withhold Dosage During Treatment.—It is my custom not to give a very large dose during the menstrual period, if I can avoid it, although I would give it during the period rather than extend the interval between the dose and the preceding one too long. While I have not had any difficulty in the way of reactions at this time, at the same time it has seemed to me that greater care should be used in dosage than during the interval.

If the patient is spitting blood, no matter how slight, I always withhold the remedy until this has passed off. I also withhold it during acute complications, such as influenza, at least for a day or two until I fully understand the nature of the infection. If I find that the patient is having an extra amount of cough, or any symptom that indicates an increased congestion in the tuberculous areas, I withhold for a day or so; but I always make it a point to reduce the dose if I withhold its administration very long beyond the time that it should be given. The necessity for this should be apparent.

One must appreciate the fact that he cannot go on in a series of doses, increasing according to rule, regardless of the length of time that has transpired since the last dose. If, through some of the various complications or conditions that I have mentioned, we are compelled to withhold the dose until after the period of decreased hypersensitiveness has passed, we must reduce the dose or run the risk of reaction.

What is the Guide to Dosage?—The chief guide to dosage is experience. The one who administers tuberculin thoughtfully and carefully and studies the remedy and the disease will soon learn the limitations within which dosage in tuberculin may be increased, and will also learn the proper interval between the various-sized doses. He will learn that it is not safe to increase

beyond a certain degree of rapidity and that the doses cannot be given too frequently or too far apart.

There is one point that I think is not sufficiently emphasized: that is, that there is just as much danger in giving doses too far apart as there is in giving them too close together. We usually take the temperature curve as our guide to dosage. I think more people depend on this than on any other one thing; at the same time, to rely on this entirely is an error. Tuberculin induces a rise in the temperature curve only when it is given in doses sufficiently large to produce an increase in the amount of toxins above what the antibodies can rapidly care for; in other words, when the tuberculin is in excess of the amount necessary to satisfy all the free-circulating receptors. Short of this we have signs which are recognizable. While I have mentioned these elsewhere, it is of sufficient importance to repeat them here. In pulmonary cases we should be put on our guard by any increase in cough or expectoration, or feeling of constriction in the chest. No matter where the lesion is situated, increased nervousness, feeling of tiredness, a tendency to ache, or a general feeling of lack of ambition, if it cannot be accounted for otherwise, should indicate an approach to the point of tolerance. Changes in the pulse rate must also be observed. Last, but not least important, the reaction which often occurs at the point of injection should be taken as a warning to go slow. Where the intracellular products are employed it is safe to withhold the dose as long as there is evidence of induration present at the site of the preceding injection, unless this has settled down to a definite hard nodule.

Observation and Control of Patient.—Before the patient is put upon tuberculin treatment it is well to observe him for a period of time. The idea of how long this period should be varies with different observers. I, personally, desire at least three days' observation before beginning the administration of tuberculin. While this is considered short by many, for one who has had a large experience, I feel that it is sufficient. For one who has not, however, I would suggest a longer period. I would further suggest that the patient during this time be under the same circumstances as he will be after treatment is begun. This period should be utilized by the physician in getting acquainted with

the patient and familiarizing himself with any particular characteristics of the disease that may be present.

This period should be sufficiently long to enable the physician to form a fairly definite idea of both the patient and his disease, so that when he begins the tuberculin he can differentiate between the symptoms due to the natural course of the disease and those due to the administration of the remedy. During this time a chart of the temperature and pulse should be carefully kept, also a record of the other symptoms present.

After treatment is begun the same careful observation should be followed. The patient who is undergoing tuberculin treatment should be led to understand that whether or not he gets well depends upon himself. Tuberculin may be administered properly, good, safe advice may be given, and yet the patient may undo all by not following out instructions carefully.

The patient should be thoroughly instructed to report every unusual symptom or any increase or diminution of symptoms. He should be taught to be honest in his co-operation. He should be told that falsification of his record may cause wrong doses to be given and may work great harm to him. I think it is especially essential that he be taught to respect the time when the dose is given. On the day and the day following, the patient should be more careful about exercising than during the rest of the time, and if the dose is very large, the second and third day following the administration of the dose should also be respected. Increased exertion on top of a large dose of tuberculin favors rapid absorption and increases the danger of a reaction.

How Tell When a Patient is Well?—This question is one that is often asked, and one to which it is difficult to give an answer. It cannot be told by the general appearance of the patient. Patients often feel well and look well many months before they are cured. The patient who is suffering from tuberculosis in its curable stage usually regains his physical vigor and normal appearance soon after the disease becomes quiescent. While this is a source of courage to the patient, it often proves to be a great detriment, because he takes the change in his general feelings to mean that he is well. Unless watched very carefully, it causes him to be oversanguine and to take foolish risks which often undo the results of treatment.

Neither can he take the diminution of symptoms to mean t[1]

he is well, because treatment may be necessary after the temperature has become normal, the cough has disappeared, and expectoration has ceased. Physical examination will show changes in the lung that we know are indicative of danger after the patient has reached his normal physical condition and active symptoms have all passed away. The summing up of the general condition and a physical examination made by an expert will probably give the best data for an opinion. I am sure that there is a tendency on the part of both physicians and patients to hurry the time when we can safely call a patient well. There is such a desire on the part of the physician to feel that he has conquered this disease and such a desire on the part of the patient to feel that he can go back to his former method of living, that, unless we stand as adamant, we will be compelled to shorten the necessary time of treatment beyond the point of safety.

There is some question on the part of students of tuberculosis as to whether we should be permitted to speak of a "cure" in tuberculosis at all. Personally, I believe that in early cases, with slight infection, we can speak of a cure with safety; but in advanced cases there is considerable question, because we know that the disease heals with bacilli remaining in the tissues, which might at any time multiply and produce renewed activity. It does not make very much difference whether we call a case an "apparent cure" or an "arrestment," as far as nomenclature is concerned, although it does encourage the patient to feel that he may sometime be cured. Whether an "apparent cure" will go on to a permanent result depends very much on the extent of the lesion, the thoroughness of treatment, and the physical and mental makeup of the patient. The patient who has a lesion that is not too extensive and has obtained a good result, if he will live rightly and devote a sufficient amount of his time to keeping up his vitality, stands very good chances of retaining his good health.

Remembering the general neurasthenic state which is so common in tuberculosis, we should endeavor to give our patients all the hope possible, both as far as securing a good result is concerned and as to retaining it. Give them carefully thought-out instructions to follow, and then give them all the assurance that following such a course will warrant.

The result of a tuberculin test can be utilized in giving an

opinion as to the condition of the patient. We know that a tuberculin reaction will remain for a certain time after the patient is well. As I said, in discussing the reaction in tuberculosis, that after a time the free-circulating receptors disappear and that only those attached to the cells remain. When this time has come about, a reaction to tuberculin should be very slight, if it does not entirely disappear. Just how long this time is we do not know. Years ago I tested my cases who were apparently cured by giving them a large injection of tuberculin (5 or 10 milligrams) from six months to a year after treatment had ceased. I usually found that those who had been classed as apparently cured or discharged failed to react.

Relative Merits of Sanatoria, Homes, and Dispensaries in the Treatment of Tuberculosis.—A thorough discussion of this would lead me too far from my subject; but the principles should be entered into with some degree of definiteness. It is not a question of what is best in the abstract, but it is a question of meeting the requirements as they are presented to us.

From my own experience in office, home, and sanatorium, I would say that there is no comparison in the treatment of patients in institutions and outside of institutions. During my sanatorium experience I have seen only one or two patients who seemed unfitted for sanatorium treatment, and these, strange as it may seem, were just the ones that needed it most. There are patients who, through fear, or nervousness, are unwilling to settle down and undergo sanatorium régime. They are, however, just as unsuited for office treatment or any other kind of treatment, and their chances of cure are practically nil under any circumstances.

Sanatorium.—I shall discuss the sanatorium first because it is unquestionably the best. The reason why the sanatorium is the ideal place for tuberculin treatment is because the patient is under absolute control. The régime of the day is regulated according to the needs of the patient, proper food is supplied him, suitable sleeping quarters are provided, and most important of all, he is where he can be seen by the physician numerous times during the day and be kept doing the things that he should do. Complications which arise are also quickly relieved, and many that would arise are prevented by the close association and cooperation that is obtained. The dose of tuberculin can be given

at the time when it should be given, and the patient can be controlled immediately following. Aside from this, the patient is removed from all of those excitements, annoyances, and interests which surround him in the home by too solicitous friends and relatives, and by business associates.

While many people believe that the sanatorium is the ideal place for the treatment of advanced cases of tuberculosis, they seem to think that it is not the place for the early cases, and by this belief allow the early case to pass on into the advanced condition before referring him to an institution. The sanatorium is primarily for the incipient case. It takes advanced cases because of necessity. It is one of the saddest things in the treatment of tuberculosis that these great institutions which have been built at an enormous outlay of money, and which are conducted at the expense of a great deal of earnestness and energy, should be devoted to restoring hopeless cases to a stage of improvement, when they might be restoring curable patients to usefulness.

Home Treatment.—While the sanatorium treatment is ideal and has everything to recommend it, owing to its cost and owing to the fact that there are not sufficient accommodations, most people must be treated in their homes. All things being equal, however, there are very few things that can be done for a tuberculous patient that will add more to his chances of cure than removing him from his home and putting him in a sanatorium where he can be guided and watched and compelled to do the things that he should do, and freed from the annoyances which surround him in the average home. It is not only necessary to tell the patient who has tuberculosis what to do, but success depends on forcing him to do it. Relatives and friends will often try to force patients, but instead of securing a co-operation they only stir up rebellion. On the other hand, friends and relatives very often try to help patients break rules, and this causes no end of confusion and annoyance during the period of treatment. The home is made for those who are well; the tuberculous individual is the exception. The sanatorium is constructed for the tuberculous; the well individual is the exception. One feels easier where he is among the majority rather than the minority.

Dispensaries.—Dispensaries must be one of the greatest factors in the treatment of tuberculosis. Among dispensaries I would

include not only special clinics but office treatment as well, meaning all forms of "ambulatory treatment."

There are great numbers of tuberculous patients who must be treated while they are working because we have no method of providing for their families if they stop work; so, unless the state takes up the matter in detail and assures the proper conditions for the treatment of all, including provision for the care of the families during the period of treatment, when the wage earner is the one afflicted, it will be necessary to treat many cases of tuberculosis while they are carrying on their work. This can be done successfully in a certain per cent of cases, but if we are to meet any great degree of success in this manner, we must take the case very early. It is impossible for a patient who is suffering from active tuberculosis to pursue his work without greatly reducing his chance of regaining health; at the same time we can treat many patients in dispensaries who are suffering from the early symptoms of tuberculosis, and bring them to a satisfactory result, even while they are working. It is a makeshift, however, and must not be considered anything more than the best method that we know to meet the exigencies of the case. It is a method of doing the best we can when better methods are denied us.

Necessity of Isolating the Open Case.—There has been a great deal said about the necessity of isolating the open cases of tuberculosis. This idea became prevalent during the time that mixed infection was so greatly feared. There is a general belief that, as soon as the tuberculous focus breaks down, the ulcerative surface is in danger of becoming infected with other bacilli. I, personally, cannot believe that this danger is so great as is so often asserted. Some physicians would have a patient with open tuberculosis wear a mask, breathing through some antiseptic. I believe it would be the ideal thing to take a patient of this kind and put him in the open air, preferably away from the centers of population, because in the centers of population the air contains more impurities and there is more danger of infection in general; but I cannot believe that the fact that a patient is suffering from a point of ulceration in the lung should be the determining cause for isolation. When bacteria are taken into the system I think they are more apt to enter through the mucous membranes than through the ulceration. I ques-

tion very much whether the fact that there is an open ulcer would make the danger from absorption of bacteria as great as would be found in a normal mucous membrane. As I said elsewhere, the fact that other bacteria are found in tuberculous ulcers does not mean that they are producing symptoms. I believe that the best place to treat all active cases of tuberculosis is in isolated sanatoria, or hospitals, but the danger of the open lesion becoming secondarily infected would not be the impelling motive in determining me to follow this course.

Who Must Administer Tuberculin?—Tuberculin will always be administered best by experts, by those who have the inclination to study it carefully and have the opportunity to observe its action closely; nevertheless, if we are ever to give the human race the benefit that can be derived from the employment of tuberculin, it must be taken up by practitioners in general. That they can do it is a self-evident fact. That they should not do it without first studying it carefully and familiarizing themselves with its dosage is also self-evident. In this little book I have endeavored to make the principles underlying the action of tuberculin and its administration sufficiently plain so that anyone who will study it carefully can administer it to the advantage of the patient; but to become expert in its use will require time and experience. I doubt whether the time has yet arrived when every family physician should take up the employment of tuberculin, but I believe that it has come to the point where every community should have a man who is capable of giving this remedy well and advantageously to the patient. Of course he may not be able to handle the more severe cases, but he can take care of the simple ones, and by knowing his limitations can secure expert help for those whom he is not able to handle. The time is not far distant, however, when the administration of tuberculin will be taught the student of medicine the same as the administration of mercury, arsenic, and morphin.

Should the Patient be Allowed to Treat Himself?—It seems almost foolish to ask this question, and I should not discuss it if it were not for the fact that I have known good physicians, men who should know better, to advise patients to buy tuberculin and treat themselves. I think anyone who appreciates the difficulty of administering tuberculin and the danger which attends its careless administration and the complexity of the disease, tuber-

culin. Soon after the patient is put on tuberculin we expect him to experience a feeling of well-being, become less nervous, sleep better, notice an improved appetite and an increase in weight, together with reduction in cough and expectoration. In such cases this is the rule and not the exception.

In treating chronic fibroid or chronic inactive ulcerative tuberculosis, we have, as a rule, patients in fairly good condition, except that they have suffered more or less from the toxins of the disease during the period of their long illness. They have already developed considerable immunity to tubercle bacilli and their toxins. The danger of reaction under such circumstances is not so great as it is in the earlier cases. Such patients are relatively easy to treat with tuberculin. The dosage can be taken up according to the schemata that I have given and can be pushed rapidly with very little danger of a reaction occurring. In these cases we must judge carefully as to our maximum dose. It is not so easy as in the earlier cases with less pronounced lesions. We must remember that we have, as a rule, a disease that is more or less widely spread. We must also recognize that there are probably some areas, especially in the chronic ulcerative type, which are prone to take upon themselves necrosis; consequently a marked stimulation should be avoided. In the chronic fibroid form the stimulation can be carried on without danger up to the point of a general reaction. In the chronic ulcerative type, I usually feel like going a little more slowly, even although the case be inactive; so I make my increase in dosage somewhat more gradual and am extremely cautious in seeing that the doses are properly spaced.

Treatment of Tuberculosis with Fever.—The cases which come under this heading are not all the same by any means. As will be seen from my discussion of fever in tuberculosis (page 127), there are many causes operating to produce a rise of temperature, but until we are able to discriminate more scientifically than we are today, we are compelled to treat these more or less empirically; but no matter what may be the cause of temperature, the method of administering tuberculin is about the same. Of course, if the case is one of mixed infection, we should, if possible, utilize the proper vaccine against the infection present, provided we know what it is. Every legitimate means possible should be used to check the temperature. Many writers suggest

the use of antipyretics in the treatment of fever. This I personally condemn on general principles. I very rarely employ any of the antipyretic drugs in my fever cases. In the first place, I can see nothing gained by so doing, except the mental effect on the patient. Once in a while, if I find that the patient is worrying unnecessarily, and I am unable to manage him by reasoning with him, then I give small doses of some of these remedies, to lower the temperature temporarily; but as a rule, I think they should be avoided, and the patient managed otherwise.

It is very important in these fever cases to give them absolute rest in bed. It is no less important to see that they do not exert themselves mentally, by reading, conversing, thinking, or worrying. They should be toned up as much as possible and encouraged to eat the right kind of food in the proper quantities. What I mean by this statement is to eat a well-balanced diet without stuffing. Another very important thing is to keep the bowels free. Autointoxication from the intestinal tract should be eliminated, and the bowels should be kept free, because great quantities of toxins are eliminated through this channel. The skin should be kept active. The patient should be kept free from chills, especially in the early morning, because a little extra chilling in the morning is very apt to be followed by a decrease in heat dissipation and extra temperature later in the day.

There is some difference of opinion as to whether tuberculous patients with fever should be treated with tuberculin, as mentioned previously. The weight of evidence is against it. My experience is in its favor. I can see no reason why a patient with fever should not be given whatever benefit can be derived from the use of tuberculin. The prevalent idea is that a patient with tuberculosis, while suffering from fever, has his bloodstream surcharged with tuberculin; but this is not true, as can readily be seen from an analysis of the condition present. In the first place, the chief cause of fever is not the tubercle toxins. If the patient were surcharged with tuberculin, as I have mentioned in previous papers, he would be having constant focal reactions in all of his foci of infection; and inasmuch as tuberculin, as it is generally conceived of, is constantly present in large quantities, this focal reaction would be cumulative. It would be constantly increasing in severity. That such a con-

dition is not true everyone knows who gives the question a moment's thought or observes local tuberculous foci while the patient is running fever. We often look into the larynx during a prolonged high fever, or into a tuberculous ulcer of the pharynx, and see no reactions present. According to the theory, of the patient's being surcharged with tuberculin, these foci of infection would certainly be highly stimulated and take upon themselves a rapid necrosis. No patient would ever be able to go through a prolonged focal reaction, such as would be produced by a constant surplus of tuberculin circulating in the blood, and live for any length of time—months, as we have often seen in tuberculosis. Nature would be repeating the same disaster which followed the use of tuberculin in the early nineties.

In the second place, in these patients who are suffering from fever, and have visible tuberculous foci, I have repeatedly injected tuberculin and observed a focal reaction following the injection when there was none prior to the injection, the same as occurs in patients who are not running fever; so, it seems to me that the chief reason that is usually given for withholding tuberculin is one that does not hold. That these patients are not able to respond readily to tuberculin in the production of antibodies is probably true. Especially is this true if they have progressed far toward the final end of the disease; but while the body cells are in fair condition, I think we can expect at least a material response theoretically, and I know we do obtain it in practice. Without question, it is as logical to administer tuberculin and expect a response as it is to expect a response from the administration of other vaccines.

I believe that when the ideal preparation for the treatment of advanced tuberculosis has been attained it will be one that takes into account the enzyme action, and an immunity not only to tuberculosis but to whatever associated pathological organisms may be present, and the proteins resulting from the liquefaction of the tuberculous tissue.

In a choice of a tuberculin to be used in the treatment of these serious cases, one of the less soluble products should be used. We desire a preparation whose absorption takes place slowly. Wolff-Eisner suggested that the injection be made between the layers of the skin itself, so as to guarantee slow but gradual absorption. The advance in dosage in such cases should also be

very gradual. It is preferable to avoid any marked focal reaction and keep well under the danger of a general reaction. While I do not have the great fear that many do of serious harm always following a focal or general reaction, at the same time I think we can accomplish our purpose best by keeping below it. The focal stimulation should be slight and well controlled. If it is, I feel that nothing but good can come from the tuberculin treatment of these patients.

Theoretically, these patients should be highly insensitive to tuberculin, but nevertheless, I increase my dose so gradually in these cases and space them so carefully and keep so far short of a focal reaction that I take no chances. It is wrong in principle to administer high dosage in these active cases. I think it is far better to advance slowly until we have reached only a moderate dose of tuberculin, and then drop back, changing to some other preparation, and running up again to a moderate dose of that preparation, and so on. By alternating in this way, usually between bovine and human preparations, I have been able to produce excellent results.

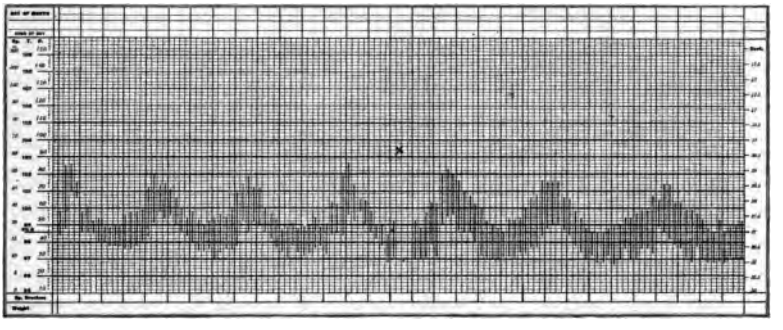
There are a certain number of fever cases in tuberculosis, in which tuberculin seems to have a marked effect in reducing temperature. I have not been able to pick these cases out to my own satisfaction, so as to be able to judge beforehand which cases will be happily affected, but I very often find, as the high dosage proceeds, coincident with some injection, a very marked drop in the temperature curve takes place. It has been my custom for many years, when this effect has been observed, to increase the dosage with extra slowness for a time, feeling that I have attained a dosage which is able to produce a maximum effect. Some stop injections when such a response has been attained and wait a week, two weeks, or a month before resuming.

It is almost impossible to treat these severe cases with any degree of success outside of an institution. While they can be treated in homes, yet it is the exception to obtain a favorable result. This is owing to the peculiar psychology of the tuberculous patient and the effect of his surroundings upon him. He cannot help but see the overanxiety of his friends, and he lacks the buoyancy and the spirit of helpfulness which pervades the air of an institution. I have said in some of my previous articles that the greatest enemy to the tuberculous patient is his friends.

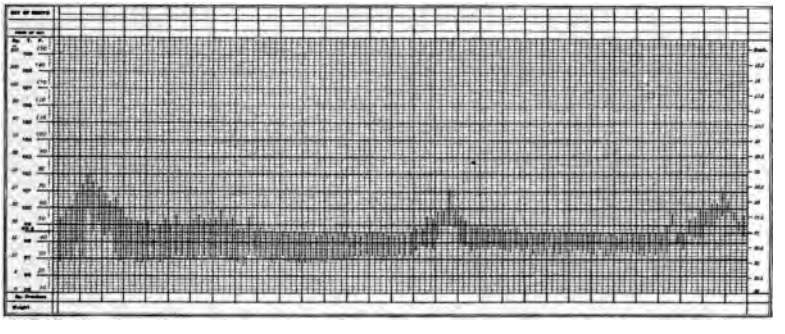
They are always giving advice; they are always making suggestions and tending to keep the patient dissatisfied. Whether they endeavor to do it or not, they are very apt to shake his confidence in what is being done for him. Harmful advice has probably killed more tuberculous patients than any other factor. If the patient with fever can be relieved of these annoyances, he is going to greatly increase his chances of cure.

A study of the accompanying charts will show some of the difficulties encountered in treating advanced tuberculosis and will emphasize the fact that the changes that occur do not necessarily occur because of the administration of tuberculin, or any other treatment. They also emphasize the fact that no one has a right to treat these severe cases unless he knows the course of tuberculosis and the action of tuberculin.

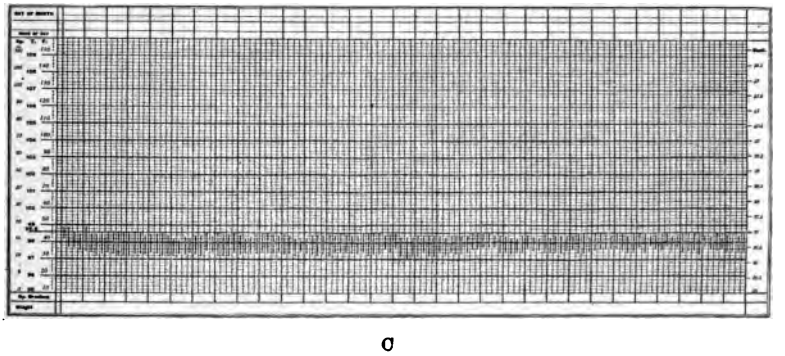
Case I (Fig. 32) is very instructive. This patient was taken with acute symptoms some three months before consulting me, although he had had slight symptoms, which were unrecognized for nine months. He spent three months in another sanatorium, during which time his temperature ran as shown in the first portion of the chart. During this time his treatment was hygienic-dietetic only, without tuberculin. He did not make improvement as he thought he should; and being discouraged, decided to change institutions. The journey was a long one and very tiresome, although it was made as easy as possible. It will be seen that the daily variations in the temperature curve, represented by the length of the lines, was greater after entering my institution than it was before. Is this difference due to the exertion of the trip, the addition of tuberculin in treatment, or to the natural course of the disease, or is it due to all? To answer this question we must analyze the chart carefully, and take into consideration the accompanying symptoms. Each of these rises in temperature was accompanied by increased cough, and most of them ended with increased expectoration. This indicates that they were due to the expulsion of broken-down caseous masses. They are to be looked upon as a part of a conservative process. Nature, in her endeavor to heal the disease, sets up an inflammatory process, casts off the necrotic tissue, and leaves a cavity in its place. Such marked rises in temperature are not necessarily due to the destruction of large areas of lung tissue. There may be a very



A



B



C

Fig. 32.—Illustrating temperature curve of chronic active tuberculosis with repeated attacks of high temperature for a period of an entire year, each line representing the variation for one day. The first part of chart 32 A prior to "x" indicates the time when the patient was in another sanatorium and not taking tuberculin. At this point he entered the Pottenger Sanatorium, and tuberculin was begun. The regularity with which the periods of high temperature came will be noticed, an attack coming on at intervals of a little more than two weeks. It will be noticed further that the swing of the temperature during the latter half of chart 32 A and the first half of charts 32 B and C shows a much greater daily variation than the earlier portion of the curve, or the latter portion of the curve. This represented a more active process and a greater amount of autolysis. It will be noticed that the attacks of temperature gradually took place at greater intervals and peared entirely. This patient was treated with tuberculin from the the Pottenger Sanatorium at "x." The tuberculin, however, was measures that helped to improve his physical condition and add to mind.

marked rise, as shown in Fig. 33, with only a small area of tissue destroyed. The cavity resulting may be so small that it cannot be detected on physical examination. We are safe in saying that these sieges of fever are entirely independent of tuberculin, because they occurred the same before as after tuberculin was administered. The increase in the daily variation was doubtless partly due to the exertion of the trip, but this hardly seems to account for it all, since the next rise came at about the usual interval and reached about the same maximum. The increase in daily variations indicates to my mind an increase of toxin absorption and

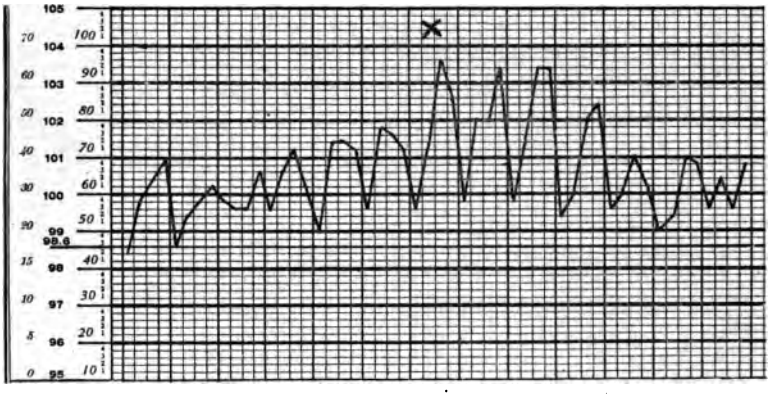


Fig. 33.—Illustrating acute elevation in temperature produced by a small ulceration in the pharynx. At point "x," a tuberculous mass in the pharynx broke down and was followed by three days of high temperature. This chart is shown to illustrate the fact that these high rises of fever are not necessarily accompanied by a great amount of destruction of lung tissue, as patients are often apt to think.

results from a greater breaking-down of tissue and an increased autolysis, with the absorption of its products. This is in keeping with the condition present. When I first examined the patient the areas of softening were quite extensive. During these temperature rises definite cavity signs appeared in the area of greatest activity, and this was followed again by a lessening of the daily variation of the temperature curve and an amelioration of clinical symptoms. In spite of the severity of the symptoms the patient went on to an arrestment. Fig. 30 (a) shows a chart of the chest on the first examination; Fig. 30 (b), a chart made ten months later.

We know this patient was suffering from tuberculosis before these active symptoms came on. Suppose he had been put on

tuberculin at that time, it probably would have been blamed for the temperature elevations. Suppose a dose had been given on the day when the temperature first began to rise, would it not have been natural to blame what followed on the remedy? Tuberculin has been blamed for many coincidences; and it often requires a careful student and close observer to determine the relationship of cause and effect.

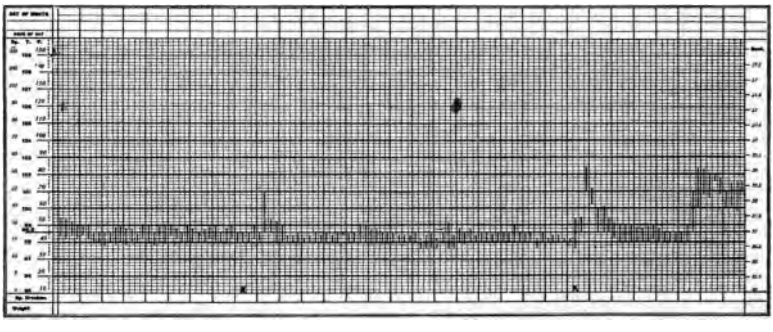
Tuberculin was begun when the patient entered my institution, after a few days' observation. The result was not an immediate cessation of symptoms. The disease ran a natural course regardless of the treatment. It was necessary that the pathological processes should continue changing until the patient was relieved of the necrotic material and until acute infiltrations had lost their inflammatory character and quieted down. Was the final fortunate result due to tuberculin? No; it was due to a combination of all the helpful measures that were employed. Fresh air, rest, diet, relief from annoying complications, tonic measures, hopeful, optimistic environment, and tuberculin all contributed their share. Tuberculin acted by increasing his antibodies and preventing the disease from spreading, and by producing a hyperemia in the foci of infection, thus bringing the antibodies in close application to the infecting bacilli and stimulating the tubercles to healing.

This is one of the types of patients upon whom doom is usually unnecessarily pronounced by our profession; but I would suggest that, wherever there is a sufficient amount of good, functionating lung left, if the patient bears the toxemia well when put under proper treatment, the patient has a chance of improvement, and probably arrestment, in spite of the acute symptoms.

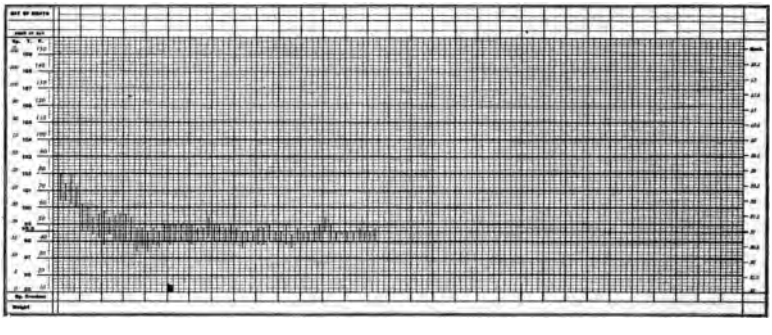
Case II (Fig. 34) is another very interesting one. The patient, after an illness of two years, had developed a widespread lesion in both lungs, with marked signs of softening through the upper lobe on the left side. Aside from the tuberculous condition, the patient suffered from an almost unbearable nervous depression. Things went well for a time, the activity in the lung gradually lessening, and the upper lobe on the left taking upon itself a high degree of contraction.

One day, without previous symptoms, the patient was taken acutely ill, with aching, prostration, and severe digestive and nervous disturbances. As influenza was somewhat prevalent at

the time, we thought it might be due to that; yet we were rather uncertain of the diagnosis from the beginning. About two months later, the second rise, noted in the chart, occurred. This was much more severe than the previous one, although the symptoms were about the same. This time the temperature began to



A



B

Fig. 34.—A, illustrating a case of moderate activity which subsided for a time and then showed increased activity marked by the various rises of temperature noted. After the second rise the patient was inclined to think that the increase in temperature must be due to the tuberculin, although the first rise in temperature occurred three days following the injection, while the second took place on the day the dose was given as noted by the "x." No tuberculin was given between the last x and square. During this time the third rise in temperature occurred, showing that the tuberculin had nothing to do with the reaction. During that portion of the curve represented by these rises in temperature, there was a marked contraction in the upper portion of the left lung, with the heart shifting entirely to the left of the sternum.

rise immediately after a dose of tuberculin had been administered. The patient at once began to suspect the remedy. Fortunately, the preceding rise had occurred four days after a dose of tuberculin had been given, which at least showed that tuberculin reactions must be very uncertain in the time of their

appearance, if both of these were reactions. This was no argument to the patient, however; so I advised a temporary change from the institution, during which time no tuberculin was to be given. While away, after a respite of about two weeks, the third rise indicated in the chart occurred. This proved to be the most serious of all. The patient now realized that tuberculin could not be the cause and voluntarily, gladly returned to the institution.

These temperature disturbances were due to the changes that were taking place in the lung. They were a part of the healing process. Nature could not heal the lung until certain necrotic material had been disposed of, and this was what occurred while she was doing it. It should also be added that, during the three or four months represented between the first and last rise in temperature, the heart shifted from its normal position to the left, so that the right border was entirely to the left of the sternum, indicating that severe changes were taking place in the upper lobe on the left, which were accompanied by marked contraction.

These cases are more than interesting. They are intensely instructive and illustrate some of the difficulties in using tuberculin.

It is well to remember that, no matter what remedy or combination of remedies is employed, the natural course of the majority of cases of clinical tuberculosis that present for treatment, is naturally downward, and unless aided by the treatment, will go on to a fatal issue.

It is further important to understand that there are no measures, which have as yet been brought forth, that can prevent advanced tuberculous processes from going through certain pathological changes. These changes are necessarily accompanied by unpleasant symptoms; and, no matter what treatment is employed, the course of the disease will be an uneven one.

Use of Tuberculin in Children.—From my discussion of infection and the period of latency in tuberculosis, the importance of treatment of the disease in childhood is self-evident. I believe that the prevention of tuberculosis, both as an infection and as a clinical disease, will come through directing our attention properly to the child and his environment.

I look forward to the protective vaccination of children against

It is a great injustice to these boys and girls to allow them to go on, become gradually weaker and weaker, and finally develop into confirmed consumptives, when the disease could be cured so easily during the early childhood period.

In the employment of tuberculin in children, I have found that they tolerate it very well. I never increase the dosage as rapidly as I do in adults, neither do I make my final dose as high; but so far, I have not had a single temperature reaction in any of the children whom I have treated, except in one instance. Until we have obtained a definite vaccine against tuberculosis, I believe that the tuberculin treatment of children offers the greatest field for the prevention of clinical tuberculosis.

Passive Immunization.—This monograph deals with active immunization; therefore I shall not discuss the various antituberculosis serums which have been produced, at any length, but since they represent the attempts to produce cure by specific remedies, they demand mention.

While the attempts at passive immunization have not as yet gained much favor, yet it seems that this field of inquiry may some day prove more fruitful. This is especially emphasized by the fact that a few men, notably Maragliano, C. Spengler, and von Ruck, have been able to produce serum with lytic qualities. This would seem to be a step in the right direction, although the nature of the disease is such that there is some question whether such preparations will be able to cure the infection. They lack the ability to produce the one essential to healing: the regular focal stimulation. The only time that we could expect this to occur is when the specific antibodies introduced by injection come in contact with bacilli, either in the foci of infection, or after escaping into the blood- and lymph-stream, causing their destruction and setting free specific toxins in sufficient quantities to produce the focal stimulation.

Maragliano, Marmorek, Paquin, Fish, and others have produced antitubercle serums which have enjoyed more or less popularity among clinicians. C. Spengler has produced a preparation which he has designated J.K. ("Immunkörper," in English "immune bodies"). This has been both praised and condemned by able clinicians. All of these preparations seem to be of some value, but disappointing to those who are expecting a perfect remedy in the cure of tuberculosis.

As yet, we must be satisfied with a remedy which will help to any recognizable degree, but we hope the time will come when such may not be true. The chief indication today in the treatment of tuberculosis is the early application of the remedies which we possess, whether it be fresh air, good food, regulated rest and exercise, tuberculin, antitoxic serum, either alone or in combination. Disappointment will be reduced to a minimum by such a course.

APPENDIX.

Owing to the importance that tuberculin has assumed in the modern treatment of tuberculosis, I consider it important that Professor Koch's own views of the remedy should be accessible to all interested in its use; therefore I offer the following translations of his original papers as they appeared in the *Deutsche medizinische Wochenschrift.*

Koch has been blamed for many things for which he was not responsible. He found it impossible to control the early administration of tuberculin and to have it given entirely according to his ideas; and while his ideas were not strictly correct, as we have demonstrated by our later work, yet, as is shown in the following papers, he had a grasp of this new subject that was truly marvelous.

The reader must bear in mind that nothing like tuberculin had ever been produced before. Koch was working in an entirely new field. He had nothing to guide him except his own broad comprehension of scientific principles, especially those of bacteriology. That he did not understand fully the action of tuberculin should not be considered strange. That there were errors in the method of dosage should not be held against him. Could he have given his grasp of the subject in all its details to the clinicians who followed out the work, there is no doubt but that the early disaster would have been averted.

His discovery of the differences in the action of this remedy on the healthy and the tuberculous has proved to be one of the most important discoveries in the modern study of tuberculosis. It has given to us the tuberculin test, which has not only enabled us to make early diagnoses of the presence of tuberculosis, but has also given us a more complete grasp of infection and when it takes place. In this way it has enabled us to understand more fully the nature of this disease and the essentials in its prevention. His descriptions of the symptoms of reaction are accurate and complete. Little has been added to his description of the focal reaction as it appears in visible tuberculosis or in hidden foci, such as those in the

lungs. One of his most serious errors was the belief that the action of this remedy was to destroy the tuberculous tissue and in that way assist in carrying off the dangerous material. This, of course, caused larger doses to to be given than would have otherwise been employed. He thoroughly understood, however, and insisted on the importance of not producing too many reactions. He recognized the improvement that occurs in both early and late lesions and described the same thing that we note today. He also recognized the difficulties that surround the treatment, particularly of advanced cases of tuberculosis, and made a strong plea for early diagnosis and immediate treatment, stating that in this way alone could the advantage of the remedy be given to the patient. He also recognized the importance of individualization and insisted that the remedy should not be given in a routine manner. He further advised the giving of the remedy in institutions under the careful intimate control of the physician.

His good reports were confirmed by a number of observers, and had it not been for the great number who tried the remedy and the great number of patients who were harmed by its wrong use, these early favorable reports would have been sufficient to establish it beyond all doubt.

If the reader will bear in mind that these were the observations of a man in a field that had not hitherto been explored and that they were given out after a period too short for accurate observation, as recognized by Koch himself, he cannot help but marvel at the wonderful grasp of the subject and the accuracy of the ideas expressed.

KOCH'S ANNOUNCEMENT OF THE DISCOVERY OF TUBERCULIN.

The following brief announcement of the discovery of tuberculin was made by Professor Koch on the 4th of August, 1890, in an address before the International Medical Congress held at Berlin. The subject of his address was "Concerning Bacteriological Investigations." After discussing the principles of prevention and detailing the results of his efforts to find methods for preventing the growth of bacteria that could be applied to the prevention of the various infectious diseases in human beings, he turns his attention especially to tuberculosis and mentions many chemical products with which he had experimented, and says:

All of these substances have proved valueless when tried on tuberculous animals.

In spite of these failures I did not allow myself to be deterred from continuing to search for remedies that would check the development of bacteria, and finally have found a substance that will check the growth of the tubercle bacillus, not only in the test-tube, but also in the animal body. All experiments on tuberculosis, as everyone knows who has experimented with this disease, are very slow; so has my experience been with this substance. Although I have been working with it now for nearly a year, I am only able to say that guinea pigs, which, as is well known, are unusually susceptible to tuberculous infection, after being exposed to the action of the remedy, fail to react to inoculations of tuberculous virus, and that guinea pigs that are already suffering from a general tuberculous infection can have the disease brought to a complete quiescence by the use of this remedy, without the body being injured in any way whatever.

From these experiments I would like to draw no other conclusions at the present time than that the hitherto doubted possibility of rendering pathogenic bacteria harmless while in the living body without damaging the organism itself has become a reality.

FURTHER REPORT ON A REMEDY FOR TUBERCULOSIS.

Robert Koch.[1]

In an address that I made several months ago at the International Medical Congress I mentioned a remedy that is able to produce immunity in animals inoculated with tubercle bacilli and to arrest further progress of tuberculous processes in animals already infected with tuberculosis.[2]

Knowledge of Remedy Reached Public Prematurely.—In the meantime this remedy has been tried on human beings, a report of which I shall make at the present time. It was my great desire to complete the investigations, to have a large experience in the use of the remedy in practice, and to have the remedy prepared in large amounts before anything was given out publicly regarding it; but in spite of all precaution, it has reached the public, and it now devolves upon me, in order to prevent misconceptions, to give forth a description of the present state of the whole affair. Nevertheless, I can only give a short description, and many important questions must remain unanswered.

Men Who Made First Trial.—The remedy has been tried under my direction by A. Libbertz and Stabsarzt Dr. E. Pfuhl. Their investigations are in part still unfinished. The necessary patients have been furnished by Professor Brieger from his polyclinic, Dr. W. Levy in his surgical private clinic. Geheimrat Fraentzel and Oberstabsarzt R. Koehler of the Charité Hospital, and Geheimrat v. Bergmann in the University Surgical Clinic. All of these gentlemen, as well as their assistants who helped in carrying out the clinical trial of the remedy, have been a great help to me, and I wish to extend my deeply felt thanks to them and to their assistants for their active interest and their devotion to the cause. Without the assistance of these men I should not have been able to progress as far as I have in this difficult and responsible experimentation. I am not able to give any further information about the origin and preparation of this remedy at the present time, because my work has not yet been completed, and I shall report on this later.

Dilutions and Method of Preserving.—This remedy consists of a clear, brownish, stable fluid. For use it must be diluted to a greater or lesser degree. After being diluted with distilled water it is likely to decompose, and bacterial vegetation is prone to develop in it and give it a cloudy appearance. When this occurs it must not be used. To avoid decomposition the solution must be sterilized by heat and be preserved in a bottle with a cotton stopper; or, what is still more convenient, the solution may be preserved with 5 per cent phenol solution. I prefer to use the fresh solution, as redistilling and adding phenol destroy the efficiency of the remedy, especially the weaker dilutions.

Method of Employing.—It is ineffective when taken by the mouth, and the

[1] *Deutsche medizinische Wochenschrift*, Extra Edition No. 46 (a), November 13, 1890.
[2] Subheadings are not in original paper.

only satisfactory method of use is by subcutaneous injection. We use exclusively in our bacteriological work a syringe that is supplied with a small rubber bulb and without a piston. This syringe is usually kept aseptic by cleansing with pure alcohol, and by this method we have not had one abscess in one thousand subcutaneous injections.

Men and Animals React Differently.—After a few experiments we have decided to inject the remedy in the back between the shoulder blades and in the thigh, because the reaction in these regions is scarcely noticeable and almost painless.

As far as the reaction on human beings is concerned, I wish to state that the reaction differs in an important point from the reaction of the remedy on the guinea pig, the animal commonly used for experiments; therefore these reactions should not be compared. Man has proved himself far more sensitive to the action of the remedy than guinea pigs. A healthy guinea pig can be injected with 2 cubic centimeters of the undiluted fluid subcutaneously, without any disturbance, while 0.25 cubic centimeter of undiluted fluid injected into human beings is sufficient to show marked disturbance.

Koch Gives Himself 250 Milligrams.—After an experiment on myself, injecting 0.25 cubic centimeter of this remedy in the upper arm, the following symptoms developed: Three to four hours after the injection I noticed a sensation of drawing in the limbs, weakness, desire to cough, difficulty in breathing, all of which rapidly increased. In five hours a severe chill set in, which lasted almost an hour; at the same time I felt exhausted, had emesis, and a rise of temperature to 39.6° C. After twelve hours these symptoms disappeared, and the temperature fell, reaching the normal point the next day. The general malaise still lasted for a few days. For a time the site of injection remained somewhat painful and inflamed. The maximum dose of the remedy that can be tolerated by a healthy man without reactions is about .01 cubic centimeter, as has been shown by many experiments. Most men react to this dose only with slight pains in the limbs and malaise, which soon pass off. In some a slight temperature reaction occurs even up to 38° C., or a little above that.

Similarity of Action in Man and Animals.—In comparing the relationship of the dose of the remedy in experimental animals and in man, there is a marked difference, but in many other particulars there is a marked similarity. The most important of these similarities is the specific working of the remedy upon the tuberculous processes, whatever kind they may be. The relationship of the experimental animals in this connection will not be gone into fully here because it would take me too far from my subject, but I shall turn at once to that most important consideration, tuberculosis in human beings.

Healthy Do Not React to 10 Milligrams.—The healthy man reacts very slowly, or not at all, as we have seen, to .01 cubic centimeter or sometimes more, as many observers have shown, but quite different are the conditions in the tuberculous. When one injects this same dose of the remedy (.01 c. c.) into one suffering from tuberculosis, there at once appears a strong general reaction as well as a focal reaction.

Symptoms of Reaction.—The general reaction consists in an attack of fever.

which, as a rule, begins with a rigor. The body temperature goes from 99°, often to 40° and 41° C., and along with it occur pains in the limbs, a desire to cough, a feeling of malaise, and often nausea. Sometimes a slight icterus appears, and also an exanthema on the neck and chest.

The attack begins, as a rule, in four or five hours after the injection and lasts from twelve to fifteen hours. Occasionally it occurs later and runs a course of less intensity. Patients are not at all harmed by the reaction, and as soon as it passes away usually feel better than before.

Focal Reaction as Shown in Lupus.—The focal reaction can be observed best in cases where the tuberculous focus is visible, for example, in lupus, in which the changes due to the specific action of the remedy show themselves in a surprising manner. A few hours after an injection under the skin of the back, some portions of the skin of the face, which are diseased, even although distant from the point of injection, and even before the beginning of the chill, begin to show swelling and redness. During the fever, the swelling increases and eventually may reach a high degree, so that the lupus patches appear here and there as brownish-red and necrotic areas. In the more sharply defined lupus patches the brownish-red areas are surrounded by a white border almost a centimeter in width; and that again by a broad bright-red circle. After the disappearance of the fever the swelling of the lupus patches again gradually disappears so that in two or three days it is gone. The lupus areas themselves become covered by crusts, formed by the oozing and drying of serum, and these soon change to scabs, which come away after two or three weeks. Sometimes a smooth red scar is formed after a single injection. Usually, however, it requires several injections to cause a complete removal of the lupus patches. Of this I shall speak later.

Lupus Heals.—Most important in this process we must emphasize the changes that have been described and that confine themselves to that portion of the skin occupied by the lupus patches. Even the smallest, the almost invisible areas, those which are almost hidden by scar tissue, become visible through the process of change in consequence of the swelling and altered color, while that portion of the lupus patch that has gone over into scar tissue remains unchanged. The observation of the action of the remedy upon lupus is so instructive and at the same time so convincing of the specific nature of the remedy that I would recommend that everyone who wishes to try it should start with lupus patients, if this is possible.

Focal Reaction in Glands, Bones, Joints, etc.—Less convincing, yet still noticeable to the eyes and touch, are the focal reactions as observed in tuberculosis of the lymphatic glands, bones, joints, etc., which show in swelling and increased pain, and in redness where the parts are superficial.

Focal Reaction in Lungs.—The reaction in internal organs, particularly the lungs, does not cause symptoms unless we look upon the increased cough and expectoration after the injection as evidence of a local reaction. In these cases the general reaction predominates; nevertheless we must also believe that the same changes that take place in the lupus patients occur here.

Value in Diagnosis.—The symptoms of reaction, already mentioned, have appeared without exception according to our observations, on the injection

of 0.01 cubic centimeter of tuberculin when a tuberculous process has been present anywhere in the body; and I believe that I am not saying too much in favor of this remedy when I express the belief that it will be a most valuable diagnostic measure in the future. I believe that it will enable one in doubtful cases of beginning tuberculosis, when a diagnosis cannot be made by either physical examination or the examination for bacilli and elastic fibers in the sputum, to determine definitely the presence of the disease. Gland affections, tuberculosis of the bones, and doubtful tuberculous conditions of the skin, as well as other forms of the disease, will be easily detected. In apparently healed cases of lung and joint tuberculosis it will help to determine whether the disease has become completely healed or if some small area still remains that will perhaps start the disease anew.

Its importance in the treatment of the disease is even greater than it is as a diagnostic measure.

Results of the Action of the Remedy on Tuberculous Tissues.—In the description of the changes caused by the subcutaneous injection of the remedy upon lupus patches, it has already been mentioned that, after the decrease in swelling and redness has occurred, the lupus tissue does not take on its original condition but seems to be partly destroyed and disappears. In some areas it has been observed that, immediately after one injection, the tissue becomes necrotic and sloughs off. In other areas a gradual disappearance and melting away of the tissue takes place, but still other injections of the remedy are required for cure.

While it cannot be stated positively just what changes occur, because the necessary histological examinations cannot be made, yet it seems fairly assured that the tissue inclosing the tubercle bacilli is destroyed, but not the bacilli themselves; in these tissues, as is shown by the swelling and redness, severe circulatory and trophic disturbances are occurring, which will destroy the tissue more or less quickly, according to the manner in which the remedy is applied.

Acts on Tuberculous Tissue, Not on Bacilli.—To repeat briefly, the remedy does not destroy the tubercle bacilli but the tuberculous tissue. With this it can be seen that the limitation of the usefulness of the remedy is very decided. It is only possible for it to act on living tuberculous tissue. In dead tissue, cheesy masses, and necrotic areas in the bones it has no effect, neither has it any effect on tissue already destroyed by the remedy itself. In the masses of tissue that have been destroyed the living tubercle bacilli may still be present. These may either be thrown off with the necrotic tissue or they may possibly, under certain conditions, produce an infection in tissue adjacent to the existing tubercles.

This action of the remedy should be especially understood in order to produce best results in its employment. First of all, living tuberculous tissue must be destroyed, and every means must be employed to separate the dead tissue as soon as possible. This cannot be done through surgical aid and must be left to the organism itself to remove slowly the dead tissue; while this is taking place, the living tissue may still be preserved from infection by the employment of tuberculin therapy.

Theory of Why the Remedy Can be Increased so Rapidly.—The fact that the remedy destroys the tuberculous and works only on the living tissue explains another of its highly specific properties: namely, that it can be given in very rapidly increasing doses. This might be looked upon as an indication that the patient is gradually becoming accustomed to the remedy; but when one realizes that the increase of doses in some three weeks amounts to five hundred times the beginning dose, then one cannot look upon this as being due to the fact that the organism accustoms itself to the remedy, because there is no analogy of any other remedy of equal strength being increased in like manner.

This property is rather to be explained by the fact that in the beginning there is much living tuberculous tissue present; consequently a small amount of the active substance is required to establish a strong reaction, but through each injection a slight amount of the tissue capable of reacting decreases, so that comparatively larger doses are required to reach the same degree of reaction as before. Within certain limitations, however, it might be considered that the tissues become accustomed to the remedy. As soon as the tuberculous patient, who is treated with increasing doses, has reached the stage where he reacts like a non-tuberculous patient, one may assume that all tuberculous tissue capable of reaction has been destroyed. After this it is only necessary to protect the patient from reinfection as long as bacilli are present in the body.

This may be done by giving small increasing doses, with occasional interruptions of treatment for a time.

Dosage in Lupus.—Whether or not this theory and the explanation of the changes depending upon it are correct, it will be necessary for the future to determine. So far, they have been sufficient to guide me in the employment of the remedy; and our experiments show the following: We shall begin again with the simplest case, namely the lupus patient. We have in almost all of these cases injected from the start the full dose of 10 milligrams. Then, after the reaction has completely disappeared, after one or two weeks, we injected again the dose of 10 milligrams and continued this until the reaction became weaker and finally ceased. In two patients of lupus of the face this treatment resulted in forming smooth scabs, after three and four injections respectively. The rest of the lupus patients have been improved, the amount of improvement varying according to the length of treatment.

Dosage in Gland, Bone and Joint Tuberculosis.—Gland, bone and joint tuberculosis have always been treated by giving large doses at even greater intervals. The result has been the same as in the lupus cases: rapid cure in early slight cases and slowly progressive improvement in the more difficult ones. Experiments with the majority of patients suffering from pulmonary tuberculosis show that patients suffering from widespread infections are much more sensitive to the remedy than those with surgical tuberculous affections.

Dosage in Pulmonary Tuberculosis.—We were obliged to reduce the usual beginning dose of 10 milligrams for our pulmonary cases, because we found that they almost invariably reacted strongly to 2 or even 1 milligram. We

also noticed, however, that we could begin with this small dose and increase rapidly until we attained the large amounts tolerated by other patients. In the pulmonary cases we usually first injected 1 milligram, and if a rise of temperature occurred, we continued the same dose daily until no reaction followed it. When no further reaction occurred, we increased the dose to 2 milligrams and repeated this until it was tolerated without reaction. Then we continued increasing the dose by 1 milligram, or at times 2 milligrams, until a dose of 10 milligrams or more was reached. This gradual method of advancing, I find especially adapted to patients that are reduced physically. If one uses the remedy in the manner described, he will be able to reach a very large dose without producing any discomfort or fever on the part of the patient. Some stronger patients that were treated from the very beginning with larger and rapidly increasing doses seemed to show more favorable results and a much more rapid improvement.

Signs of Improvement in Pulmonary Tuberculosis.—The reaction of the remedy showed itself in the pulmonary cases generally by slight increase in the cough and in the amount of expectoration. After the first few injections this gradually decreased, and in the favorable cases finally completely disappeared. The purulent sputum gradually assumed more and more of a mucoid character. The number of bacilli (only such patients were taken for treatment whose sputum contained bacilli) decreased as a rule only when the sputum had become mucoid in character and the weight had increased. The bacilli disappeared sometimes entirely, but from time to time reappeared again until the sputum had completely disappeared. At the same time the night sweats ceased, the appearance of the patient improved, and the weight increased.

Incipient Cases Healed, Advanced Ones Improved.—Those patients who were treated with the remedy in the incipient stage of tuberculosis were, as a rule, relieved of all symptoms within from four to six weeks and could be regarded as healed. Also patients, who had cavities that were not too large, greatly improved and were nearly cured. Only such patients whose lungs contained many and large cavities failed to receive objective improvement, although the sputum and subjective symptoms disappeared. *From these experiences, I feel assured that incipient tuberculosis can be unquestionably cured.*[3] This may also be said of some cases of the advanced stage.

Difficulties of Cure in Advanced Tuberculosis.—Patients with large cavities, who usually suffer from other complications, such as the appearance of pus-producing micro-organisms in their cavities, cannot expect to obtain lasting results from the use of the remedy, because of the irremediable pathological changes in other organs; but exceptionally, these cases have shown a lasting improvement after treatment. From this we can draw the conclusion that the remedy affects the original process of disease in these patients in the same manner as in the cases that are less advanced; but that there is

[3] This opinion cannot be expressed unreservedly, because up to the present time our experiments do not exclude the possibility of relapses occurring, but we may assume that even should relapses occur they can be cured again like the first attack. It is also possible that, according to the analogy in other infectious diseases, those who are cured may remain permanently immune. This also, however, will have to be looked upon as an open question at the present time.

not the same possibility of removing the destroyed tissue and the secondary suppurating processes.

This naturally brings up the question whether or not surgical aid in the treatment might not be used to the advantage of the patients treated with this remedy.

Must Not be Given in Routine Manner and Should be Reinforced in Every Way Possible.—I would especially strongly urge that this remedy should not be used in a routine manner in the treatment of all cases of tuberculosis. The treatment will be easiest in the incipient pulmonary cases and in simple surgical affections. In all other forms of tuberculosis, however, medical skill should be employed to its fullest measure. The action of the remedy should be reinforced by careful individualization and by employing every measure that will aid its action.

Best Given in Institutions.—In many instances I have been of the impression that the nursing that the patient has received has had a very favorable influence upon treatment, and I should prefer to give the remedy in institutions that are especially adapted to the care of the patients, where they can be closely observed and receive the necessary attention. How much those measures that have usually been regarded as useful in the treatment of tuberculosis, such as living in mild climates, open-air treatment, special diet, etc., can contribute to the advantage of the patient combined with the new method, cannot be stated at this time, but I believe that these measures, combined with the new remedy, will be of advantage in many cases, especially in far-advanced ones and those that are in a state of convalescence.[4]

Early Diagnosis and Early Treatment Essential to Success.—The most important point in this new method of therapy lies in employing the remedy at the earliest moment possible. We should make it our object to treat the incipient stage of pulmonary tuberculosis, because it is at this time that we expect the best action of the remedy; therefore we cannot urge too strongly that the practicing physicians should in the future, more than they have in the past, do everything in their power to diagnose tuberculosis in its earliest stage. So far, the discovery of tubercle bacilli in the sputum has been considered simply as a matter not altogether uninteresting, but of secondary importance; and while a diagnosis could have been made by the examination of the sputum, at the same time it has not been made to work to the advantage of the patient. This fact has only been too frequently the cause of neglect in the examination of the sputum, and in recent times we have found in numerous cases that patients have been to several physicians without their sputum having been examined. This must change in the future. A physician who does not use all measures at his command to diagnose tuberculosis in its earliest stage, especially the one who fails to obtain the knowledge that would be derived by the examination of suspicious sputum, will be accused of serious neglect, since the life of his patient may depend on this early diagnosis and immediate specific treatment. In doubtful cases the physician should assure himself of the presence or absence of tuberculosis by means of the tuberculin test injections.

[4] We have had very little experience from which to draw conclusions in the treatment of tuberculosis of the brain, larynx, and miliary tuberculosis.

This new scientific method can be made a real blessing to suffering humanity only when the large majority of cases can be taken for treatment in the early stage of tuberculosis; and by treating them at this time, the disease will be prevented from assuming the serious advanced forms that have been a never-ceasing source of new infection. I wish to state that I purposely avoid giving in this address statistics and descriptions of cases, because the physicians whose patients we have used for experiment will report on these themselves and I do not wish to anticipate their observations.

A STILL FURTHER REPORT ON A REMEDY FOR TUBERCULOSIS.

Robert Koch.[1]

Koch's Views Confirmed by Others.[2]—Since my announcement of my experiences with a remedy for the treatment of tuberculosis two months ago, many physicians have received the remedy and are now in a position to give an opinion of its properties from their own personal experiences. So far as I am able to judge from the publications that have appeared and from the private letters that I have received, my observations have received complete confirmation. That the remedy has a specific action upon tuberculous tissue, in consequence of which it is a delicate and sure test for tuberculous infection and of special value in cases where the diagnosis is doubtful, has been confirmed by all. With reference to the curative action of the remedy, while the time of treatment has been comparatively short, yet most observers reported that more or less improvement had occurred. Quite exceptionally it was maintained that the remedy hastens the tuberculous process and is injurious, not only in far-advanced cases, in which one will admit it without question, but in others as well. I, personally, have had the opportunity during the past month and a half to collect further experiences relative to the diagnostic and curative effect of the remedy on one hundred and fifty patients in the Moabit Municipal Hospital, suffering from tuberculosis of the most diverse forms, and can only say that everything that I have seen recently corresponds with my earlier observations, and that I have no reason for changing what I previously stated.[3]

So long as it was only a question of substantiating the correctness of my statements, it was not necessary to know what the remedy contained or how it was produced. On the contrary, the less that is known of the remedy itself, the more impartial will be the test. But now that the test has been made in sufficient cases, as it appears to me, and the importance of the remedy has become known, I recognize that the next task is to study the remedy as it has been employed up to this time and see if it is possible to apply the same principle to other diseases. It will be at once recognized that these problems demand the full knowledge of the nature of the remedy; therefore I consider that the time has come to give forth the necessary facts.

Before I take up the description of the remedy itself, I believe that I can

[1] *Deutsche medizinische Wochenschrift*, 1891, No. 3.

[2] Subheadings not in original paper.

[3] In reference to the permanency of the cure, I would like to add that two of the patients that I had previously designated as healed have been readmitted into the Moabit Hospital for further observation and that now for three months they have shown no bacilli in their sputum, and the physical signs have gradually completely disappeared.

give a better understanding of the manner in which it acts if I describe briefly the observations which led me to its discovery.

Observations Which Led to the Discovery of Tuberculin.—When one inoculates healthy guinea pigs with a pure culture of tubercle bacilli the inoculation wound closes up and apparently heals within a few days. In the course of ten to fourteen days, however, a hard nodule appears, which breaks down and forms an ulcer. This remains until the death of the animal. It is quite different, however, when a guinea pig that is already tuberculous is inoculated. Animals that have been inoculated from four to six weeks previous are best suited to this purpose. In one such animal, however, the inoculation did not heal in the beginning, but small nodules appeared, and within one or two days showed characteristic changes about the point of inoculation. Around the point of inoculation it became hard and took upon itself a darker color, which did not confine itself to the immediate point of inoculation but spread to the surrounding tissues for a distance of from ½ to 1 centimeter. When the succeeding dose is administered it shows very distinctly that the skin showing the alteration is necrotic; and it is eventually cast off, a small superficial ulceration remaining, which usually heals quickly and permanently without the regional lymph-glands becoming involved. The inoculated tubercle bacilli also act very differently upon the skin of a healthy guinea pig from what they do upon one infected with tuberculosis. This characteristic action is not entirely confined to living tubercle bacilli but also occurs when dead bacilli are used, whether the bacilli be destroyed as I attempted in the beginning, through low temperature of long duration, or by boiling, or through the action of chemicals.

Solutions of Ground Bacilli Act Differently in Healthy and Tuberculous Guinea Pigs.—After these characteristic actions had been discovered, I followed them in every direction; and I found that pure cultures of tubercle bacilli that had been killed, ground up, and mixed with water could be injected under the skin of healthy guinea pigs in large amounts without producing anything beyond a local suppuration.[4] Tuberculous guinea pigs, on the contrary, were killed by the injection of very small amounts of such cultures of dead bacilli within from six to forty-eight hours after the dose had been administered. A dose that is not sufficiently large to kill an animal often produces an extensive necrosis of the skin in the neighborhood of the site of injection. If the solution of dead cultures of bacilli is diluted still further so that it appears only slightly opalescent, then the animal remains alive; and if the injections are carried on with intervals of one or two days, a remarkable improvement in the condition of the animal takes place.

Solution of Ground Bacilli Has Curative Action.—The ulcerating inoculation wound becomes smaller and eventually forms a scar such as never occurs without such treatment. The swollen lymphatic glands become smaller, the nutrition of the animal improves, and the diseased process becomes quiescent if it is not too far advanced and the animal does not go rapidly down to death as is usual.

These observations furnished me a basis for producing a remedy against

[4] Such injections belong to the surest and simplest means of producing local suppuration free from living bacteria.

tuberculosis. The practical application of such a solution of dead tubercle bacilli is made difficult by the fact that the tubercle bacilli are not readily absorbed from the point of injection, neither do they disappear in other ways, but lie for a long time unchanged, producing a large or small point of suppuration.

That which acts in a healing manner upon the tuberculosis process must be a soluble substance that is extracted from the tubercle bacilli by the body juices and carried very rapidly into the blood and lymph-stream, while that which produces the suppuration goes into solution very slowly and remains back apparently in the tubercle bacilli.

Tuberculin Finally Produced.—The problem of greatest importance that presented itself for solution was to determine whether or not the active healing substances could be separated from the bacilli on the outside of the animal body. This task took a great deal of time and much pains before I finally succeeded in producing a forty to fifty per cent glycerin solution, containing the active substance of the tubercle bacilli. It was a solution produced in this manner with which I carried on further experiments on animals, and finally on men, and which I have given to other physicians to repeat my observations.

The remedy then with which the new attempt at healing tuberculosis has been carried on is a glycerin extract of pure cultures of tubercle bacilli.

Content of Tuberculin.—In this simple extract we find, besides the active healing substance, other substances that are soluble in fifty per cent glycerin; therefore we find a certain amount of mineral salts, some coloring matter, and other unknown extracts. Some of these substances may be separated very easily. The specific curative substance is especially insoluble in absolute alcohol and can be precipitated by it, not in the pure state, but in combination with other extractives that are also insoluble in alcohol. The coloring matter may also be separated from it; so it is possible to prepare the extract as a dry colorless substance containing the active principle in a much more concentrated form than the original glycerin solution. As far as the practical therapeutic employment of the remedy is concerned, the purified glycerin extract seems to have no special advantage, because the substances that are contained in the original solution seem to be inactive as far as the human organism is concerned; therefore the refining process only necessarily increases the cost of the remedy.

Active Principle a Protein.—At the present time we can only make suggestions regarding the nature of the active healing substance. It seems to me to be of protein derivation but belongs to the group of so called "toxalbumins," because it stands high temperatures and dialyzes readily. The quantity of the substance present in the extract is to all appearances a very small one. I should estimate it as a fraction of 1 per cent.

Theory of the Action of Tuberculin.—If my hypothesis is correct, we are dealing with a substance whose activity in the tuberculous organism far transcends that which is known even of our strongest-acting remedies. Necessarily, many hypotheses have suggested themselves whereby we account for the action of the remedy upon tuberculous tissue. Without feeling absolutely

certain, I am of the opinion that the best explanation is as follows: The tubercle bacilli produce during their growth in living tissue, likewise in artificial cultures, certain substances that influence the living elements surrounding them, that is, the cells of the various organs. In these tissues is found a substance that in a certain concentration destroys protoplasm or so changes it that it is transformed into a condition that has been described as coagulation necrosis by Weigert. In this tissue that has become necrotic the tubercle bacillus often finds nutritive conditions so unfavorable that it is no longer able to grow and finally dies. In this way I explain the surprising fact that one finds many bacilli in fresh tuberculous diseased organs; for example, in the gray nodules that are scattered through the spleen or liver of a guinea pig; while they are rare, or even disappear entirely when the spleen has become enlarged and white, and in a condition of coagulation necrosis, as one often finds it when the tuberculous guinea pig is allowed to go on to death. When individual bacilli are separated by some distance they will not produce necrosis; for, as soon as necrosis has reached a certain degree, the growth of the bacilli, and therefore the production of necrotic substances, ceases, and a mutual compensation takes place, which works in such a manner that the growth of the individual bacillus becomes very limited, as, for example, in lupus and scrofulous glands. In such cases the necrosis usually extends only over a portion of a cell, which, then, by its enormous growth, assumes the peculiar form known as the giant cell. In this conception I accept the theory of Weigert who first gave this explanation of the conditions that produce the giant cell.

Now, if one should artificially increase the amount of necrosis in the tissues surrounding the bacilli, the necrosis would become widespread, and the nutritive conditions for the bacilli would become much more unfavorable than they usually are. Sometimes the tissues becoming necrotic in large areas are wholly destroyed and cast off. Where this occurs the bacilli that are enclosed are cast out of the body at the same time. Sometimes the bacilli are so disturbed in their growth that they are much more easily destroyed than under ordinary conditions.

It appears to me that the action of the remedy consists in the production of such changes as are here described. It contains a certain amount of substance that produces necrosis, of which a certain-sized dose, even in those who are healthy, injures certain tissue elements, perhaps white corpuscles, or the cells that lie near the bacilli, and in this way produces the whole peculiar symptom-complex, known as reaction. It requires a very much smaller amount of the remedy to produce a widespread necrosis of cells and the general symptoms that accompany this process in the patient who is already tuberculous, especially in those areas where the tubercle bacilli are growing and have already impregnated their surroundings with necrotic substances. In the manner here mentioned, at least provisionally, we may explain the specific influence that this remedy produces upon tuberculous tissue, when given in definite doses, as well as the possibility of increasing this with such unusual rapidity; and also the unusual curative properties that the remedy has manifested.

INDEX.

A.

Allergy, 29
Animal experiments, showing immunizing effect of tuberculin in, 100
Animals, artificial immunity in, 61
Antibodies contained in red blood-cells, 126
  in active tuberculosis, 38
  in healed tuberculosis, 38
  in latent tuberculosis, 38
  specific, how found, 39
    likened to national army, 39
  tuberculosis, both fixed and free in the blood, 5
Antitoxins in production of immunity in tuberculosis, 4, 37, 67–73
Antituberculin increased by tuberculin, 125
A. T. O., Koch, schema for employing, 164
  table showing method of diluting, 159
Autolysis, symptoms accompanying, 140
  temperature curve of, 139
Autotuberculin therapy, 74

B.

Bacilli affect tuberculous and non-tuberculous differently, 5
  finding of, not necessary for diagnosis of tuberculosis, 2
  living, in production of immunity in man, 62
  mobilizing of, a myth, 22, 98
  reduction of, not necessary to improvement, 190
Bacillus, discovery of, furthered diagnosis, 1
Bandelier and Roepke's method of dosage, 108
B. E., Koch, schema for administering, 165
  table showing method of making dilutions of, 160
Béraneck, tuberculin of, 154
B. F., Denys, schema for administering, 164
  table showing method of making dilutions of, 159
Bouillon Filtrate (Denys), 153
Bovine tuberculin introduced by Spengler, 154

C.

Calmette, conjuctival test of, 47
Cases illustrating curability of tuberculosis in childhood, 212
    difficulties in tuberculin treatment, 83, 206–211
Chart, advantages of graphic temperature, 185
Chest, minute examinations of, necessary for comparison, 184
Childhood, infection in, 30, 53–56
  symptoms of tuberculosis in, 212
Children respond well to tuberculin treatment, 212
  use of tuberculin in, 211–214

Chill, cause of, 141–143
Complications heal more rapidly under tuberculin, 120
prevented by use of tuberculin, 119
Conjunctival reaction a test of activity, 13
specificity of, 50
test, 47
Cubic millimeter as unit of dosage, 162, 163
Curability of early active tuberculosis, 66
of latent tuberculosis, 66
Cure, how to tell when it is effected, 194
natural, why it fails to heal, 116
psychological effect of term, 195
where it fails spontaneously, use tuberculin, 73
Cures, greater percentage of, when tuberculin used, 115
Cutaneous tuberculin test, 29

D.

Denys, Bouillon Filtrate (B. F.), 153
Diabetes and tuberculin, 87
Diagnosis, differential, between active, quiescent, and healed tuberculosis, made by cutaneous test, 34–37
early, subcutaneous test in, 22
furthered by discovery of tubercle bacillus, 1
by tuberculin, 2
Dispensaries, 197
Dosage, Bandelier and Roepke's method of, 108
cubic millimeter unit of, 162, 163
danger points in, 164
harmonizing of different theories of, 109–114, 178, 179
how to avoid errors in, 171
in early tuberculosis, 201
limit of, for tuberculin test, 17, 26, 28
method of increasing, 173
Pottenger's method of, 108
principle of increasing, 166, 167
repeated small, compared with toximmunity, 178–180
Sahli's method of, 108
Trudeau's method of, 107
warning signs of, 193
what is guide to, 192
when to withhold, 192
Wright's opinion of, 106
Dose controlled by extent of focal reaction, 184
following reaction, 191
Koch gives himself 250 milligrams, 18
maximum, individual, 180
repeated small, regards immune response main factor of cure, 109
small, disregards focal simulation, 110
Doses, interval between, 175, 180

E.

Ear, tuberculin in tuberculosis of, 123
Eczema and tuberculin, 124
Enzymes as cause of fever, 129
as factor in reaction, 73
Erlich's theory of tuberculin reaction, 3
Examinations of chests should not be made too frequently, 185

Exertion, mental and physical, affect temperature, 145
Experimental proof of value of tuberculin, 124
Eye, tuberculin in treatment of tuberculosis of, 124

F.

Fever an index of reactivity of body cells, 128
  cause of, 127
    in tuberculosis, 133
  due to tuberculin, explanation of, 111
  effect of, on growth of micro-organism, 127
  in its relationship to tuberculosis, 127
  not a sign that patient is surcharged with tuberculin, 130, 203
  produced by enzymes, 129
  reduced by tuberculin, 205
  treatment of, with tuberculin, 202–211
  when begin tuberculin in, 200
Focal stimulation disregarded in repeated small doses, 110

G.

Genitourinary tuberculosis and tuberculin, 122

H.

Healing, focal reaction main factor in, 183
  of tuberculosis complicated, 69
  often follows decided focal reaction, 183
Heart disease and tuberculin, 87
Hemorrhage and tuberculin, 86
  initial, may be followed by negative tuberculin reaction, 13
Home treatment, 197
Hypersensitiveness a precipitation reaction, 91
  after doses, 175–180
  an agency of defense, 92
  defined, 90
  developed in treatment due to faulty application, 93
  first observation of, made by Koch, 91
  how produced, 94
  to tuberculin, 92
    how prevented, 95

I.

Immunity, artificial, in animals, 61
  character of, following dose, 175–180
  complete, not produced by tuberculin, 101
  evidence of, in tuberculosis, 58–60
  in human beings, 61
  natural development of, 56
  production of, in man by use of living bacilli, 62
  to late infection produced by early infection, 60
Immunization of children by von Ruck, 62–64
  passive, 214
Infection, immunity develops with, 56–60
  in tuberculous families, 54
  spread of, prevented by tuberculin, 118
  time of, determined by tuberculin test, 5

Infection—*Continued.*
tuberculous, in country districts, 56
in hospital children, 55
takes place in childhood, 30, 53–56
Inflammation, tuberculosis heals by, 115
Injection, reaction at site of previous, 172
site of, 172
time of day, 169
Intestine, tuberculosis of, and tuberculin, 121

K.

Kidney, tuberculin in tuberculosis of, 122, 123
Koch, Bacillen Emulsion (B. E.) of, 154
followers of, who saved tuberculin, 100
Old Tuberculin (O. T.) of, 153
rules suggested for use of tuberculin by, 96, 220–231
theory of tuberculin reaction of, 3
Tuberculin (R.) of, 154
unjustly censured for failure of tuberculin, 99

L.

Larynx, tuberculosis of, and tuberculin, 120
Latency, 64–66
danger of, 65
not harmless, 5
Latent tuberculosis compared with inactive tuberculosis, 10
dangerous, 9
Lignières' test, 46
Lymphatic glands and tuberculin, 121
Lysin theory of action of tuberculin, 4, 37, 67, 73

M.

Marmorek's theory of tuberculin reaction, 3
Meyer and Schmitz show that red blood-cells contain antibodies, 126
Mixed infection, 85, 130
and tuberculin, 132
curve of, 140
Spengler's and Kitasato's methods of examination of sputum for, 131
symptoms accompanying, 141
Moro's percutaneous test, 45

N.

Necrosis, prevention of, 133, 134
Needle, care of, 169
Negative phase, 76, 77
Wright's respect for, 109
Nephritis and tuberculin, 87

O.

O. T., Koch, schema for employing, 164
table showing how to make dilutions of, 159

P.

Paterson, experiments of, in autotuberculin therapy, 75
Patient, control of, necessary, 193
  how tell when well, 194
  should he treat himself, 199
P. E., Spengler, schema for administering, 165
  table showing method of making dilutions of, 160
Petruschy's method of giving tuberculin, 181
Pickert and Lowenstein show that serum of patient receiving large tuberculin neutralizes tuberculin, 125
Pirquet, von, cutaneous test of, 29
  and Schick's theory of tuberculin reaction, 3
Pleural effusion and tuberculin, 120
Pottenger's method of dosage, 108
Prognosis, value of cutaneous test in, 40
Protein, bacillary, action of tuberculin depends on, 68
P. T. O., Spengler, schema for employing, 164
  table showing method of making dilutions of, 159
Pulse, rapid, and tuberculin, 86
P. V., Spengler, schema for administering, 166

Q.

Quiescent tuberculosis, signs of, 10.

R.

Reaction, conjunctival, 48
    negative, 49
  cutaneous, fails through the presence of tuberculosis, 31
    importance of, 30
    in active tuberculosis, 34–37
    in healed tuberculosis, 34–37
    in quiescent tuberculosis, 34–37
    interpretation of, 33
    negative, 33
    positive, 32
    shows that infection occurs in childhood, 30
    specificity of, 31
    what affected by, 33
  focal, 20, 73
    as control of dosage, 184
    desirability of control of, 112
    healing follows, 112
    main factor in healing, 183
    maintained in treating early and inactive tuberculosis, 201
    often overcomes chronic temperature, 183
    pains from, not common, 20
    to be avoided in advanced active tuberculosis, 204, 205
    when to avoid, 183
    when to produce, 183
  from bovine and human tuberculin differs, 148
  general, 18
    and focal, each present without the other, 112
  healing stimulated by, 24
  local, 18
    at site of previous inoculation, 172

Reaction—*Continued.*
percutaneous, character of, 45
phenomena of, 71
secondary, characteristics of, 148
traumatic, 32
tuberculin, cause of, suggested by Ehrlich, 3
by Koch, 3
by Marmorek, 3
by von Pirquet and Schick, 3
by Wassermann and Bruck, 3
by Wolff-Eisner, 4
varies according to condition of patient, 11, 37
Records, minute, of chest examination necessary for tuberculin treatment, 184
Relapses, tuberculin prevents, 124
Rigor, cause of, 141–143
Ruck, von, immunization of children by, 62–64
watery extract of, 154

S.

Sahli's method of dosage, 108
Sanatorium the place for curable cases, 197
treatment, advantages of, 196
Schemata, 162
Specificity of conjunctival reaction, 50
of cutaneous reaction established by post-mortem evidence, 31
of tuberculin, 6
Spengler, Perlsucht Emulsion of, 154
Perlsucht Tuberculin (P. T. O.) of, 154
T. B. V. and P. V. of, 154
Symptoms accompanying active, progressive tuberculosis not stopped by tuberculin, 189–190
autolysis, 140
mixed infection, 141
amelioration of, following use of tuberculin, 189–190
of tuberculosis in childhood, 212
Syringe for administration of tuberculin, 25, 167–168
method of using, for accuracy, 167
necessity of washing carefully, after doses, 168

T.

T. B. V. and P. V., Spengler, schema for administering, 166
Technic of cutaneous test, 41
Temperature chart, advantages of, graphic, 185
chronic, of low grade often overcome by focal reaction, 183
curve caused by human and bovine tuberculin differs, 148
characteristics of, in tuberculosis, 137, 138
due to tuberculin reaction, 148
factors interfering with regular, 143
influenced by sleep and amount of bed covers, 144
by weather conditions, 144
in tuberculosis, 136
normal, 136
of autolysis, 139
in mouth influenced by vasomotor disturbances, 144
influenced by bath, 143
by hearty meal, 143
by mental and physical exertion, 145

Temperature chart—*Continued.*
of mixed infection, 140
menstrual, 148
premenstrual, 147
proper interpretation of, necessary in giving tuberculin, 145
rules for accurate measurement of, 25
wide daily oscillations of, 129
Therapy of advanced active tuberculosis, 133, 134
Toximmunity, advantages of, over repeated small doses, 173, 174
compared with repeated small doses, 178, 180
production of, regards both antibodies and focal stimulation, 110
Toxins, moderate doses of, produce rise in temperature; large doses, a fall, 128
soluble, more apt to produce reaction, 201
T. R., Koch, schema for administering, 165
table showing method of making dilutions of, 160
Treatment, advantages of sanatorium, 196
cannot be safely shortened, 194–195
duration of, 181
indiscriminate, not favored, 84
of chronic fibroid tuberculosis, 202
ulcerative tuberculosis, 202
of early tuberculosis, 201
of fever with tuberculin, 202–211
Petruschy's method of, 78
tuberculin, length of, 78
shortens, 120
Trudeau immunizes animals by living avian bacilli, 61
method of dosage of, 107
Tuberculin, action of, 4, 37, 73–76
depends on bacillary protein, 68
modified by existing infection, 4
administration in fever, 200
intravenous, 156
oral, 156
subcutaneous, 156
advantages of, in artificial use over autoinoculation, 74
after-course of, advisable, 182
all preparations of, similar in action, 151
an active immunizer, 82
and diabetes, 87
and heart disease, 87
and hemorrhage, 86
and nephritis, 87
and organic diseases, 87
and rapid pulse, 86
are there patients who cannot be treated with, 191
artificial administration of, superior to natural, 116
as test of cure, 196
Béraneck, 154
Bouillon Filtrate (B. F.), Denys, 153
bovine, 154
cannot be best given according to rule, 178
cases illustrating effect in treating children with, 212–213
cause of fever produced by, 111
choice of, 151
coincident fever often blamed on, 209
complications heal more readily with, 120
consider solubility in choosing preparation of, 152

Tuberculin—*Continued.*
cubic millimeter unit of dosage of, 162, 163
demands close observation of patient, 105
difficult of administration, 76
dilutions of, for subcutaneous test, 21
disagreement of friends injures, 105
disaster of 1890–91, 96
discussion of phenomena following doses of, 175–180
dosage of, in early tuberculosis, 201
early disaster due to severe focal reaction, 113
effect of, on early diagnosis, 2
employment demands accurate knowledge of tuberculosis, 104
endangered by faulty use, 102
evidences of therapeutic value of, 115
experimental proof of value of, 124
factors preventing adoption of, 96
for subcutaneous test, 21
guide to dosage of, 192
how to avoid errors in dosage of, 171
to judge value of, 189, 190
hypersensitiveness to, due to faulty employment, 93
how prevented, 95
in course of treatment, 92
immunizing poser of, shown by animal experiments, 100
in eczema, 124
in lymphatic glands, 121
in mixed infection, 132
in pleural effusion, 120
in treatment, 51
in tuberculosis of ear, 123
of eye, 124
of intestine, 121
of larynx, 120
individualization in use of, necessary, 114
initial dose of, 173, 174
interval between doses of, 175–180
judged by best results obtained, 103
lack of knowledge of, injures, 101
maximum dose of, an individual matter, 180
method of administering, 155
of diluting, 157
of giving, more important than preparation, 152
of increasing dose of, 173, 174, 175
misunderstood, 52
neutralized by serum of tuberculous treated by large loses of tuberculin, 125
no set length of time for treatment with, 182
not a poison, 4, 51
cause of chronic temperature, 130
necessary that improvement follow use of, 189, 190
observation of patient before beginning, 193
(O. T.), Koch, 153
patient not surcharged with, during fever, 203, 204
percentage of cures increased by, 116
Perlsucht Emulsion, Spengler, 154
(P. T. O.), Spengler, 154
Petruschy's method of giving, 181
prevents complications, 119
necrosis, 133
relapses, 124

Tuberculin—*Continued.*
spread of infection, 118
produces histological tubercle, 69
reaction, 17
cause of, suggested by Ehrlich, 3
by Koch, 3
by Marmorek, 3
by von Pirquet and Schick, 3
by Wassermann and Bruck, 3
by Wolff-Eisner, 4
curve, characteristics of, 148
diagnostic value of, 11
does not locate the lesion, 15
fever not necessary for, 23
focal, 20
pain not common in, 20
general, 18
in active tuberculosis, 12
in advanced tuberculosis, 12
in healed tuberculosis, 11
interpretation of, 14
local, 18
due to combination of tuberculin and antibodies, 11
may be negative after initial hemorrhage, 13
nature of, in quiescent tuberculosis, 12
negative when infection present, 14
Sahli's fear of, 23
secondary, 149
reactive capacity of patients to, differs, 10
relatively of greater value in advanced tuberculosis, 117
routine administration of, not best, 163
shortens time of treatment, 120
should patient administer it to himself, 199
specific action of, follows laws of hypersensitiveness, 4
specificity of, 6
statistics of therapeutic value of, 117
suffers from lack of knowledge of tuberculosis, 103
T. B. V. and P. V., Spengler, 154
technic of administering, 151
test a test for tuberculosis antibodies, 5
conjunctival, 47
a test of activity, 13
contraindications for, 48
repetition of, 48
technic of, 47
tuberculin used in, 47
cutaneous, 29
prognostic value of, 40
technic of, 41
theory of, 37–38
theory on which, differentiates between active, quiescent, and healed lesions, 37
tuberculin used in, 43
determines time of infection, 5
information furnished by, 7
percutaneous, 45
unreliability of, 45
reliability of, 8
same patient may react to one and not to another, 8

Tuberculin test—*Continued.*
subcutaneous, 16
choice of tuberculin for, 21
contraindications for, 22
danger of, compared with exploratory incision, 16
fear of, 16
healing follows, 24
in early tuberculosis, 22
method of dosage in, 26, 27
preliminary observation for, 24
technic of, 25
ten milligrams limit of dosage in, 17
value of, 5
time of day making injections of, 169
tray, 170
treatment, contraindications for, 80
indications for, 80
length of, 78, 79
of fever, 202–211
use of, in treatment of children, 211–214
used in conjunctival test, 47
in cutaneous test, 43
when spontaneous cure fails, 73
value of each dose of, should be known, 161
Virchow's opposition to, 98
watery extract, von Ruck, 154
what it cannot do, 52
when to withhold, during treatment, 192
when used increases percentage of cures, 115
who shall administer, 199
Tuberculins all the same qualitatively, 4
differ according to the medium on which bacilli grow, 160
to virulence of bacilli from which they are made, 160
not standardized, 161
Tuberculosis, active and conjunctival reaction, 49
diagnosed by cutaneous reaction, 34–37
more common than believed, 8
tuberculin reaction in, 12
advanced active treatment of, 204–205
cases illustrating successful treatment of, 83, 206–209
treated best in institutions, 205
tuberculin reaction in, 12
antibodies both fixed to cells and free in blood-stream, 5
attitude of profession toward, 17
chronic fibroid, treatment of, 202
inactive, ulcerative, treatment of, 202
curability of early active, 66
early dosage in, 201
treatment of, 201
evidences of immunity to, 58–60
healed, diagnosed by cutaneous test, 34–37
nature of tuberculin reaction in, 11
heals by inflammation, 115
infection of, occurs in childhood, 53–56
lack of knowledge of, harms tuberculin, 103
latent, curability of, 66, 67
dangerous, 9
demands treatment, 66
diagnosed by cutaneous reaction, 35

Tuberculosis—*Continued.*
may not react to tuberculin, 6
open, necessity of isolating, 198
original focus of, never kills, 110
quiescent, nature of tuberculin reaction in, 12
signs of, 10
rapidly progressive, and tuberculin, 83

V.

Virchow opposes tuberculin, 98

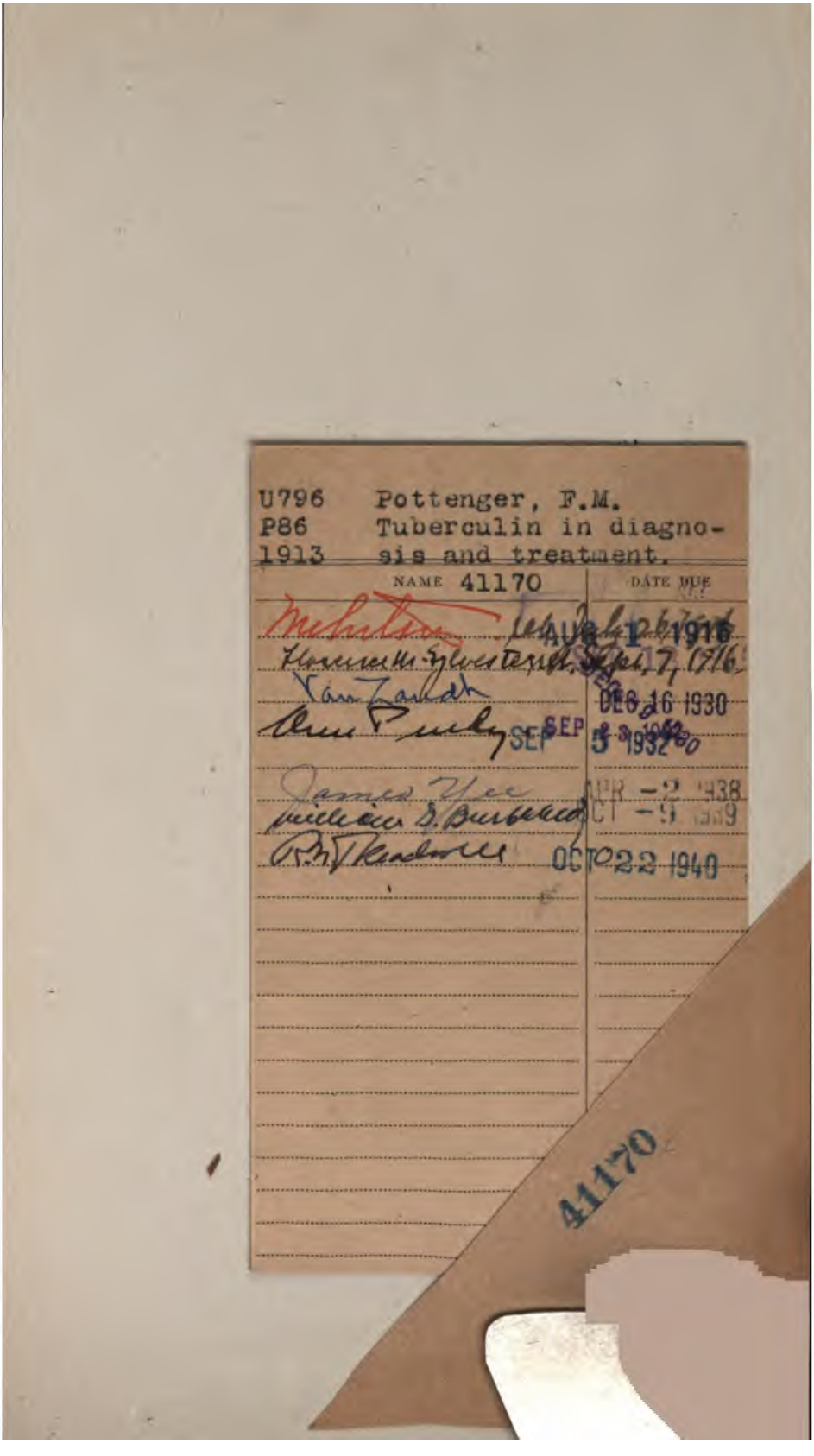
W.

Wassermann and Bruck's theory of tuberculin reaction, 3
Watery extract, von Ruck, 154
schema for administering, 165
table showing method of making dilutions of, 160
Wolff-Eisner, conjunctival test of, 47
theory of tuberculin reaction of, 4
Wright's method of dosage, 106

LANE MEDICAL LIBRARY

To avoid fine, this book should be returned on
or before the date last stamped below.

AUG 1 1916
SEP 18 1916
DEC 16 1930
SEP 5 1932
APR -2 1938
OCT -9 1939
OCT 22 1940



U796 Pottenger, F.M.
P86 Tuberculin in diagno-
1913 sis and treatment.

NAME 41170

DATE DUE

AUG 1 1916
SEP 7 1916
DEC 16 1930
SEP 3 1932
APR -2 1938
OCT -9 1939
OCT 22 1940

41170